Katherine Keyes expert witness report

I. Background and Qualifications

A. Summary

I am an Associate Professor of Epidemiology at Columbia University, specializing in substance use and substance use disorders epidemiology.

B. Education

I received a Masters degree in Public Health from Columbia University in 2004, and a PhD in Epidemiology from Columbia University in 2010.

C. Field of specialty and employment history

My field of specialty is substance use and substance use disorders, as well as related comorbidity, focusing on psychiatric disorders, and consequences of substance use including intentional and unintentional injury. After receiving my PhD in Epidemiology in 2010, I completed a post-doctoral fellowship in Epidemiology at Columbia University from 2010 through 2012, and then was recruited by Columbia University to join the faculty in 2012 as a tenure-track Assistant Professor. I was promoted to Associate Professor in 2016. I also hold academic appointments at various other universities. I am a Research Assistant Professor at the University of Michigan, and an Adjunct Associate Professor at the Society for Health and Research at Universidad Mayor in Santiago, Chile.

D. Research areas and publications

I have published 225 peer-reviewed articles and book chapters, more than 60 of which are first-authored. Much of this research has been published in the leading, highest impact epidemiology, psychiatry, and substance use journals, including in *Pediatrics, JAMA Psychiatry, Lancet Psychiatry, Nature Communications, British Medical Journal, British Journal of Psychiatry, American Journal of Psychiatry, American Journal of Epidemiology,* and *International Journal of Epidemiology*, among others. My articles have been cited in numerous disciplines, including psychiatry, epidemiology, public health, and pediatrics. My *h*-index ranges from 43 (Web of Science) to 60 (Google Scholar)[1]. Currently, 50 of my articles have been cited more than 100 times; 15 of my articles have been cited more than 200 times; and 4 have been cited more than 500 times. Since obtaining my doctoral degree, I have led numerous and sustained extramurally funded grants as Principal Investigator, and have successfully competed for grant funding from the National Institutes of Health to conduct my research. I have received numerous grants from Columbia University for my work, including the Calderone Prize for junior faculty, and the Tow scholarship (awarded to high-achieving mid-career scientists). I serve as a co-Investigator on numerous federally-funded grants both at Columbia and at other institutions (including University of Michigan and New York University).

I have published two textbooks on epidemiological methods, and I am well-qualified to assess the literature on opioid-related harm. The first is *Epidemiology Matters: A New Introduction to Methodological Foundations*, published by Oxford University Press in 2014, which is currently being used to teach graduate students about epidemiological methods in more than 20 universities. The second is *Population Health Science*, also published

[1] An h-index is a measure of productivity and research impact. It is the median level of correlation between number of peer-reviewed papers and the number of times each paper has been cited for a given scholar. As such, an h-index of 60 indicates that I have published a median of 60 papers that have been cited at least 60 times. Benchmarks for h-indices vary; at Columbia University department of epidemiology, the standards for promotion are an h-index of at least 15 for promotion to Associate Professor, and at least 25 for promotion to professor. My h-index is more than twice that needed for a full professor rank in my department at Columbia University, indicative of high productivity and impact.

by Oxford University Press, which details the theoretical and methodological foundations of the science of public health.

My expertise on opioid-related harm includes large scale survey data and vital statistics analyses, as well as the development of theories, hypotheses, and publishing findings concerning the role of macro-social factors in producing opioid epidemics. Specifically, I have extensively used high-quality survey data collected at the national level in order to estimate incidence, prevalence, and trends in risk factors for opioid use disorders, and trends in opioid use. Further, I have utilized data on fatal and non-fatal overdose to estimate determinants of variation in overdose across communities. My work focuses on community-based sampling strategies as well as hospital records to document epidemiolocal correlates and determinants of risk. I have published 19 peer-reviewed journal articles on opioid use and related harms (and many more on drug use disorders more generally), detailing trends over time in prescription opioid misuse, birth cohort trends in nonmedical opioid use and overdose, and risk factors for non-medical prescription opioid use, and consequences of use across developmental periods, including consequences related to overdose. I have particularly focused on elucidating drivers of population-level trends, including literature reviews, synthesis, and empirical analyses of urban-rural differences in nonmedical opioid use and overdose. Thus, I am well-qualified to review the literature and offer conclusions based on the evidence and my own experience. I have no conflicts of interest in making these assessments, and have never consulted on behalf of any entities that stand to profit from drug or medical device sales.

E. Professional Organizations/Professional Societies/Awards

I have assumed national and international leadership roles in my areas of expertise. I am currently on the executive board of the *Society for Epidemiological Research*, to which I was elected by my peers. I am on the executive board of the *World Psychiatric Association Epidemiology and Public Health* section, and, in 2018, hosted the bi-annual meeting of the section at Columbia University. I serve on committees and boards for numerous other societies, including the *Research Society on Alcoholism* (program committee), *International Association of Population Health Science* (program committee), and *Society for Research on Adolescents* (dissertation award committee) among others, and each year actively participate as a symposium chair and speaker on multiple workshops and roundtables at each of these meetings. In 2017, I was asked to join a National Academies of Sciences committee on accelerating the progress to reduce alcohol-impaired driving and contributed to the consensus report with evidence-based policy recommendations.[1] I have served on numerous NIH review committees for several study sections and institutes and was asked to join the Social Science and Population Studies section as a standing member, to commence in 2019. Finally, I serve as Associate Editor of the journal *Drug and Alcohol Dependence* and as field editor for *Alcoholism: Clinical and Experimental Research*, both of which are highly regarded journals for original research on alcohol and drug use disorders and related harms.

My career achievements have been recognized with numerous awards. I was given the early career achievement award by three scientific societies (*Research Society on Alcoholism, American Psychopathological Association, and the World Psychiatric Association Epidemiology and Public Health Section*), as well as the *NIH Office of Disease Prevention Early-Stage Investigator* award, a competitive award recognizing two scholars per year, from any NIH institute, who are poised to become leaders in the field. I am invited as a speaker nationally and internationally, with approximately 40 invited lectures, including 15 in 2017 and 2018.

II. Opinions

For the detailed reasons stated in this report, I have the following opinions:

- Medical use of opioids is associated with the development of opioid use disorder at higher rates than were reported by drug manufacturers; rates of opioid use disorder increase with the dose and length of opioid use among medical users.
- The opioid supply increased dramatically in the United States beginning in the early 1990s, and a direct consequence of the increased supply of opioids was an increase in the incidence and prevalence of opioid

use disorder among both medical patients and non-patients (among non-patients, over-supply of opioids were diverted to illicit marketplaces).

- The expansion of non-medical prescription opioid use would not have occurred without the widespread availability of prescription opioids that were originally dispensed for medical uses, often in greater quantities and doses than needed, leaving a surplus of opioids that could be diverted for non-medical uses.
- Prescription opioid use is causally associated with harm among adolescents, especially when it is initiated at critical developmental windows for adolescence.
- Prescription opioid use is also causally related to subsequent heroin use. Approximately 80% of heroin users in the last two decades used prescription opioids before heroin use, and while the proportion of prescription opioid users who progress to heroin use is relatively small, even small increases in the proportion who progress can explain the majority of increases in heroin use in the United States. Because the heroin supply has been contaminated with high-potency synthetic opioids (e.g. fentanyl) since approximately 2013, prescription opioid use is also causally related to the increase in synthetic opioid morbidity and mortality since prescription opioids precede the transition to heroin, including heroin contaminated with fentanyl.
- Prescription opioid overdose increased exponentially in the United States in the past 20 years, and these increases strongly correlate with rates of prescription opioid supply for medical use both in terms of geographic variation in supply as well as year-to-year variation, in both observational and quasi-experimental studies, providing an evidence base that suggests that supply and availability of opioids caused an increase in the rate of prescription opioid overdose. Prescription opioid overdose is higher in Summit and Cuyahoga County than national rates in the US.
- In addition to fatal overdose, other consequences to communities affected by opioid oversupply include non-fatal overdose; neonatal abstinence syndrome, which is higher in Summit and Cuyahoga County than the national average; and physiological dependence, which occurs among essentially all people who are exposed to sufficient dose and duration of opioids.
- Prescription opioid and other opioid mortality disproportionately affected economically deprived areas; however, the available evidence indicates that economic conditions played a relatively small part in increased opioid-related morbidity and mortality. The driving force in increasing opioid-related morbidity and mortality was, and continues to be, access to and wide-spread availability of opioids.
- Compared with other commonly used pain relievers such as non-steroidal anti-inflammatory drugs (NSAIDs), the health and addiction consequences are substantially and significantly greater from opioids than from NSAIDs, including for cardiovascular events, fractures, and falls, as well as poisoning and overdose.
- Abatement of opioid-related consequences in Summit and Cuyahoga County is critical. In this report I describe the need for Medication Assisted Treatment (MAT) availability for the population of opioid dependent users, as well as high-priority populations including those in jail/prison, pregnant women, and families involved in the child welfare system. I describe the burden of harm and the numbers needed to expand access to these populations.
- Further, I outline other abatement strategies with known effectiveness, including naloxone distribution and access as well as fentanyl testing, surveillance, and test strips.

To summarize, there is compelling evidence of harm from the oversupply of prescription opioids, both for medical users, and to non-medical users because of diversion. These harms include opioid use disorders and overdose; these harms are greater than other pain relief drugs, and are causally related to additional harms from opioids including transition to heroin addiction. Relief and abatement are critically needed, including expanding access to medication assisted treatment, overdose prevention and harm reduction, as well as addressing the current crisis of fentanyl overdose through testing and surveillance.

III. Methodology

A.1. Definitions of methodological and substantive terms

Before detailing the scientific evidence that underlies my opinions, it is useful to describe a set of terms that I will be using throughout the report.

Prescription opioids. Medications indicated for the control of moderate to severe pain, and include natural opioid analgesics (morphine and codeine), semi-synthetic opioid analgesics (oxycodone, hydrocodone, hydromorphone, and oxymorphone), synthetic opioids (methadone), and synthetic opioid analgesics (e.g. tramadol and fentanyl).

Medical use of prescription opioids. Medical use will refer to use of prescription opioids based on a physician prescription, and use as directed by a physician.

Non-medical use of prescription opioids. Non-medical use refers to both using prescription opioids more often or longer than prescribed, or use of prescription opioids without a prescription. These definitions are commonly used in large scale surveys of prescription opioid use in the population. For example, the instrument for the National Household Survey on Drug Use and Health asks "Have you ever, even once, used any prescription pain reliever in any way a doctor did not direct you to use it?" Examples given to respondents include use without a prescription, use in greater amounts, more often, or longer than prescribed, or use in any other way that a doctor did not direct. This question and similarly worded questions on other large-scale surveys are the commonly used assessment of non-medical prescription opioid use. Some reports also label this as "prescription opioid misuse", however I will use the term 'non-medical prescription opioid use' for consistency. Non-medical prescription opioid use is also referred to as *'opioid misuse'* in much of the literature, although definitions and measurement assessments differ in what is included as opioid misuse. For example, some measures of opioid misuse include using opioids for euphoria, or for the experience or feeling that using opioids caused, which could conflate some medical and non-medical reasons for use.[2] Throughout the report I will be specific to the measurement of non-medical opioid use, and refer to non-medical use of prescription opioids when referring to use other than a way that a doctor prescribed, regardless of the motivation for the non-medical use.

Opioid misuse. For the purposes of this report, opioid misuse is synonymous with "non-medical prescription opioid use", and refers to use of prescription opioids in ways other than prescribed, including taking more than prescribed, or using prescription opioids that were not prescribed by a physician. As noted above, however, throughout this report I will detail the definitions that studies use when using the term "misuse" to highlight variation in the definition in the literature, and will primarily rely on the term "non-medical use of prescription opioids" when discussing the literature and findings related to use of opioids that is outside the medical oversight and prescription of a physician.

Physical opioid dependence. Individuals who use opioids can develop tolerance to the medication. Tolerance develops when the endogenous opioid system acclimates to the medication and more is needed to produce the desired effects. Dependence on opioids also occurs in medical uses of opioids, in which more opioids are needed to achieve the desired effects (tolerance) and when the cessation of opioids produces symptoms of withdrawal and craving for opioids. Physical opioid dependence can occur even at low doses, but is increased with dose and duration of use. Physical opioid dependence is not addiction or opioid use disorder, and should not be conflated with such disorders. Physical opioid dependence is expected even when opioids are used medically; yet physical opioid dependence is clinically challenging, and increases the risk for transition of patients to opioid use disorders and addiction. Tolerance and withdrawal are symptoms of opioid use disorder, but are neither necessary nor sufficient for a diagnosis of opioid use disorder, as described below.

Harms due to opioids. Harms due to opioids include non-fatal overdose, neonatal abstinence syndrome use due to opioid use, dependence, and opioid use disorders (see below), and deaths that are directly attributable to opioid use as designated on death certificates.

Opioid use disorders. Opioid use disorder is a diagnosis in the Diagnostic and Statistical Manual of mental disorders (DSM), as well as the International Classification of Disease (ICD). It is important to point out from the outset of this description that opioid use disorder is distinct from the physical opioid dependence (defined above) that would be expected to occur with repeated administration of opioids. Medical use of opioids would be expected to produce symptoms such as tolerance (needing more opioids to achieve the same effect) and withdrawal (uncomfortable and painful physical and psychological symptoms during cessation of opioids). However, opioid use disorders, involve a maladaptive pattern of use from which there are serious consequences in domains of functioning. The fourth version of the DSM was published in 1994, and included two diagnoses that together comprised opioid use disorders: opioid abuse and opioid dependence. Opioid abuse was diagnosed if there was "a maladaptive pattern of use leading to clinically significant distress or impairment" as indexed by at least one of four symptoms in a 12-month period including recurrent failure to fulfill major role obligations (e.g. repeated absences from work, neglect of children), recurrent use in physically hazardous situations (e.g. driving under the influence), continued use despite social or interpersonal problems because of use (e.g. arguments with family, physical fights while intoxicated), legal problems due to use. Opioid dependence was diagnosed if there was "a maladaptive pattern of use leading to clinically significant distress or impairment" as indexed by at least three of seven symptoms in a 12-month period including tolerance (needing more of opioids to achieve intoxication or desire effect, or diminished effect with continued use of the same amount of opioids), withdrawal (defined via a substance specific syndrome), using the substance in larger amounts or over a longer period than intended, persistent desire or unsuccessful efforts to cut down or control use, physical or emotional problems caused or exacerbated by use, excessive time spent in activities to obtain or use substance, and social/occupational/recreational activities given up in order to use. Tolerance and withdrawal are symptoms of opioid use disorder, but they also occur in patients use opioids as prescribed in medically supervised setting, and thus tolerance and withdrawal alone are not sufficient for a diagnosis of opioid use disorder. Opioid abuse in DSM-IV also could not be diagnosed if criteria for opioid dependence were met. Data analysis using these diagnoses were often combined such that "opioid use disorder" was any diagnosis of opioid abuse or dependence. In the fifth revision to the DSM (DSM-5), published in 2013, several changes were made to the diagnosis. Opioid abuse and dependence criteria were combined for a single diagnosis of "opioid use disorder"; craving was added as a criterion (strong desires to use opioids); and "legal problems" was removed as a criterion. Diagnoses could be made at three levels: mild (2-3 symptoms); moderate (4-5 symptoms); and severe (6+ symptoms). In this report, I will be specific about whether DSM-IV or DSM-5 criteria were used in research assessing opioid use disorders. Opioid use disorder diagnoses are sometimes made based on ICD-9 and ICD-10 criteria. These criteria overlap substantially with DSM criteria, although ICD-9 included craving as a criterion for diagnoses whereas DSM-IV did not.

Addiction. Addiction is a concept often synonymous with opioid use disorder, but is not a clinical term available for diagnosis in major nosologies such as the DSM or the ICD. However, it is used frequently in the literature with various definitions, sometimes used to refer to physical opioid dependendence, but most often to refer to individuals who use opioids non-medically for their euphoric effect, and/or those who exhibit harms due to opioids that include important social, occupational, physical, and relationship impairments due to non-medical prescription opioid use. Because addiction is not a well-defined clinical diagnosis, throughout this report I will detail how "addiction" is defined in studies that use the term, and will focus on opioid use disorder primarily when discussing the literature on opioid-related harms.

Overdose. An injury to the body caused by poisoning from excessive opioid use. Symptoms of an overdose include shallow breathing, weak pulse, loss of consciousness, and constricted pupils. An overdose can be fatal or non-fatal.

Incidence. Incidence, or incidence rates, refers to new diagnosis over a population at risk for developing the outcome. For example, the incidence of opioid use disorder would be an assessment of newly developed cases among those who did not previously have a diagnosis.

Prevalence. Prevalence, or prevalence rates, refers to the total number of cases over a well-described population. For example, the prevalence of opioid use disorder in a given year would be estimated as the total number of cases of opioid use disorder (both new and persistent) over the total population size.

Relationship between incidence and prevalence. Prevalence and incidence are both used to demonstrate total burden of harm for health outcomes in the United States. Prevalence rates provide essential information regarding the counts of cases that are a combination of new and existing over time, and can be used to assess risk factors and correlations. Because prevalence includes both new and existing cases, the prevalence of an outcome in a given population at a given time is estimated by the incidence rate plus the average duration of the outcome. Prevalence is critical for determining total burden of health outcomes, especially to assess surveillance of trends over time. Incidence of an outcome is critical for documenting emerging epidemics and the existence of new cases. The assessment of risk factors for incident cases is of interest because it can establish the extent to which exposures generate new cases of a health outcome; risk factors for prevalent cases combine risk factors for new cases plus risk factors for cases that are chronic or un-resolving. This report will include information on both incidence and prevalence, with efforts made to specify the differences between the estimates.

Diversion. Diversion of opioids has been defined in various ways across a variety of sources, including the transfer of opioids obtained through legal medical sources to the illicit marketplace. I will use a broader definition of diversion, which is consistent with numerous other scholars, which is that diversion occurs when opioids are diverted from their intended recipient, for example, when traded for monetary value, barter, or for no cost among family and individuals in a shared social network, when sold for money by illicit dealers and traffickers.

Systematic review. A systematic review carefully summarizes existing evidence on a specific topic. Systematic reviews provide defined search criteria in the peer-reviewed literature, report articles that were included an excluded with transparent criteria, and the relevancy of the studies included for generating conclusions about the research question under consideration. Judgements are made from systematic reviews about the quality of evidence that has been gathered, existing gaps in the research, and quantitative as well as qualitative assessments of the strength of the evidence. The purpose of a systematic review is to summarize the strength of the evidence for a particular topic.

Meta-analysis. Meta-analysis quantitatively combines evidence across studies to provide summary estimates for the association between exposures and outcomes. Meta-analyses take published and in some cases unpublished estimates from across studies and uses them to generate a summary estimate with more statistical power because of the combined effect across studies. Methods in meta-analysis allow researchers to weight studies based on quality or informativeness, such that studies that have a higher quality of evidence can be given a greater weight in determining the summary estimate. Meta-analyses are considered a higher level of evidence than single studies, because while single studies may have particular bias or confounding, a large number of studies analyzed together generally provide a more rigorous estimate of the true relationship. Studies that are included in a meta-analysis should be sufficiently similar to warrant summarizing estimates of magnitudes of association together, while simultaneously estimating heterogeneity in effect sizes across studies.

Confounding. Confounding occurs when risk factors that are causes of the outcome are unequally distributed between exposed and unexposed persons. Study estimates that are confounded do not reflect the true causal relationship between exposures and outcomes. For example, consider the relationship between prescription opioid use (exposure) and heroin use (outcome), which is evaluated in this report. Men are more likely to

both use prescription opioids and to use heroin. Thus, the estimate of the relationship between prescription opioid use and heroin use is confounded by sex, and control for sex in statistical analyses of the relationship would be appropriate.

Bias and misclassification. Bias can arise in the study design and analysis of epidemiological studies from a variety of sources. Among the most pernicious forms of bias in epidemiological studies is information bias, also called misclassification. That is, when reporting on the presence of substance use disorder among a group of research subjects, any substance use disorder that is missed among research subjects would be characterized as misclassification. With regard to opioid use disorders, the presence of disorder is often underestimated due to misclassification of opioid dependent individuals as non-dependent. Misclassification is magnified when opioid use disorders are not assessed with structured, validated instruments for measurement of opioid use disorder, or with objective assessments of the presence of opioids and other drugs through urine toxicology.

Further, misclassification has been assessed in vital statistics designations of causes of death for which opioids may be involved.[3] Death certificate procedures vary by state and local region within state, in terms of whether they are completed by a medical examiner or conorer, and with regard to the quality and completeness of the information presented on the death certificate. One source of potential misclassification bias is in the designation of the type of opioid that caused ovoerdose. Approximately one fifth of opioid overdose deaths are coded on death certificates as unknown with respect to the specific opioid that caused the death. Methods have been developed to impute data on type of opioid when the opioid is unknown (for example, Ruhm et al. 2018[4] used a probit model that predicted type of opioid based on other information on the death certificate, when estimating the association between economic factors and overdose death. Robustness analyses using the corrected and uncorrected versions of unknown or undetermined opioid causing death indicated that statistical results were robust whether the unknown opioids were reclassified or not. This is one indication that while some deaths that involve opioids are misclassified, death certificate reports are reliable indicators of the burden of opioid-related death in the United States, especially with regard to trends in opioid-related death. Throughout this report I will assess the impact of opioid use disorder and opioid-related death via misclassification in order to provide a rigorous review of the evidence.

A.2. What role does epidemiology play in describing opioid-related harm

Epidemiology is the "science of understanding the causes and distributions of population health."[5] To understand causes and distributions, epidemiologists examine the dynamic nature of populations and how health and disease arises within them, as well as the conditions that shape population health over time and space, including policies, practices, and politics that create conditions that improve or deteriorate population health. Whereas a physician examines each patient that enters her clinic, asking what caused a particular health outcome for this particular patient, an epidemiologist looks over the landscape of a population across time to determine why the burden of a particular health outcome is greater or worse in some areas, at some time points, and among some subgroups, and queries what in the social, political, and environmental landscape create the distributions and their changes over time.

Epidemiology has played a key role in understanding the increases in opioid use and related harm in the population. A central role for epidemiology is in surveillance. Using a variety of methods, epidemiologists examine the incidence and prevalence of opioid use, non-medical opioid use, and consequences of use such as opioid use disorders, overdose, and neo-natal abstinence syndrome across time and place. Epidemiological studies have documented changes in the incidence and prevalence of these outcomes across time, heterogeneity in the incidence and prevalence by state and county, and correlations with factors such as availability and access of opioids, individual-level risk factors, and policy changes. Further, epidemiological studies are critical in documenting the longitudinal short- and long-term consequences of inter-individual variation in risks associated with opioid use. That is, epidemiological studies compare individuals with and without specific opioid use patterns to determine the longitudinal associations between use and health and mortality. Epidemiologists are particularly skilled at controlling for and examining confounding, which is commonly used to mean common causes of an exposure and an outcome that are being assessed. When

confounding is present, groups are not comparable to each other on causes of the outcomes other than exposure. For example, individuals who do and do not use opioids (both medically and non-medically) may have different underlying risk factors for long-term health and mortality risks, and thus the science of epidemiology involves testing the extent to which relationships between exposures and outcomes are robust to statistical controls for these risk factors. Epidemiologists use a variety of methods to control for confounding in estimates, including statistical controls in regression models, propensity scores estimation, randomization, and quasi-experimental methods such as instrumental variable analysis. In summary, the role of epidemiology in describing opioids is to quantify the extent to which use and harms associated with use are changing over time, the determinants of those changes, as well as individual-level risk factors for non-medical use and harm.

Key to epidemiological assessments is the concept of risk factors. Risk factors are variables that, when present, increase the frequency with which an outcome occurs, but need not be necessary or sufficient for the occurrence of the outcome to be fully determined. A useful example is that of cigarette smoking and lung cancer. It is now widely accepted that cigarette smoking is a cause of lung cancer. However, not all cigarette smokers will develop lung cancer (thus, cigarette smoking is not sufficient to cause lung cancer in and of itself), and not all lung cancers occur among smokers (thus, cigarette smoking is not fully necessary to cause lung cancer). Yet, cigarette smoking increases the risk that lung cancer will occur, and thus it is considered a cause of lung cancer if there are cases of lung cancer that would not have occurred in the absence of cigarette smoking. I will apply the same "risk factor" framework to my assessment of the causes of the opioid crisis, considering factors to be causes of opioid use disorders, overdose, and related harm if some cases would not have occurred in the absence of prescription opioid use. This framework does not preclude or ignore that addiction and related harms are multi-factorial in their etiology, but rather asks whether there are cases for which the outcome would not have occurred without the presence of prescription opioid use.

A.3. Methodology for review of the evidence

A.3.1. Literature search strategy

I undertook a review of the evidence to assess the impact of opioid sales and distribution in the United States on opioid use disorders and addiction, overdose, diversion, transition to heroin, as well as the evidence-based recommendations for abatement of opioid use disorder through medication assisted treatment, harm reduction, and surveillance. In order to conduct this literature review. I relied on methodology that is considered standard in the scientific process, as outlined below.

First, I used search terms in the peer-reviewed literature related to the areas of my literature review. For this I used PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), a search engine produced and maintained by the US National Library of Medicine National Institutes of Health. Full texts of scientific articles produced in the searches were available by subscription through my faculty appointment at Columbia University. Search terms were entered into the search bar, and titles were then reviewed for relevance to each particular topic. Full-texts were then reviewed to determine if there was original data and information within each specific category that related to topics covered in the expert report. Full-texts articles in journals that are indexed in PubMed are considered to be reputable; journals that are indexed by PubMed have long histories of publication, and are included only if they meet well-recognized standards including editorial oversight by recognized experts in the field as well as peer-review by experts.

Peer-review is considered to be the gold-standard of the scientific process; peers are experts in the field who evaluate each submitted paper for flaws in design and logic and make quality assessments. However, while peer-review is an important component of the scientific process, peer-review is not sufficient alone to establish quality and validity of a scientific study. Limitations in the peer-review system have long been documented in the scientific literature, including that inadequate study design and statistical analysis flaws go unnoticed by peer-reviewers,[6] publication biases lead to scientific studies with statistically significant results more likely to be published and cited than studies with null results,[7] incorrect and inaccurate reporting of

study outcomes and results,[8] and the pernicious influence of conflicts of interest among study researchers that leads to bias in the conduct and reporting of research.[9] For example, the British Medical Journal found that financial ties of study investigators were associated with a 3-fold increased in positive study results, based on analysis of 190 clinical trials that were published in 2013.[10] While the scientific literature has made advances in the peer-review system through rigorous development of reporting guidelines, more clarity and specificity in the reporting of conflicts of interest, and the inclusion and compensation of editors who additionally review papers for quality, peer-reviewed studies should still be rigorously monitored when deciding whether to cite them for a particular piece of evidence. In this report I have included studies assessed by peer-review and done additional review of the articles based on my own expertise in order to discern whether they meet quality benchmarks. As an associate editor for multiple scientific journals, I have over a decade of experience evaluating the quality of the scientific literature for publication. I have served as a peer reviewer for hundreds of scientific papers in the field of substance use and substance use disorder epidemiology, and am thus well qualified to review the literature for papers that demonstrate a sufficient level of quality to be included in a review of the evidence.

Second, within full-text reviews, additional studies that were relevant to each topic were identified based on the reference lists and citations of articles identified by PubMed search. Reference lists were reviewed and additional articles extracted based first on title review for broad relevance to the topic of study. Then, full texts were again reviewed, and included in the literature review of the article contained original information that was relevant to the topic under study.

Finally, I also included the non-peer-reviewed "gray" literature, as it was relevant to the topics under study. Specifically, I reviewed government and agency reports from the following: Centers for Disease Control and Prevention, Substance Abuse and Mental Health Services Administration, and Agency for Healthcare Research and Quality. These reports included assessments of time trends in opioid poisoning and overdose, rates of opioid use disorder, and hospitalizations for opioid-related causes. Other gray literature was included based on review of reference lists from PubMed searches when relevant to the topic of study.

A.3.2. Levels of evidence evaluated

Throughout this report, I make assessments of the rigor of the evidence that has been used to support conclusions and opinions. There are two general categories of studies that I will include in this report: the first are studies that examine associations, and the second are studies that examine trends over time.

With regard to studies that examine associations, I considered the following levels of evidence. First, I considered randomized controlled trials to be a high level of evidence, given that the possibility of confounding and bias to influence the results is most likely to be mitigated in randomized controlled trials. For example, in sections on evidence for medication assisted therapy (MAT) as part of an abatement strategy, I included randomized controlled trials that assessed the evidence for MAT for remission of opioid use disorders. However, for many of the associations reported in this statement, randomized controlled trials are unfeasible or unethical. For example when assessing the transition from prescription opioid to heroin use, it is highly unethical and would never be considered to randomize individuals to high levels of prescription opioids in order to observe the transition to heroin once prescription opioids were tapered. Indeed, for much of the literature cited in this report, randomized controlled trials would never be conducted. Furthermore, randomized controlled trials are not de facto strong evidence, as publication bias, conflicts of interest, specifics of the study design, study population assessed, outcome measurement, study duration, statistical power, and rigor of statistical anlaysis should all be considered when evaulating a particular randomized controlled trial for the level of evidence that it brings to a particular study question. For example, many randomized trial of prescription opioids are uninformative for relevant question of opioid use disorder incidence due to the lack of systematic measures of opioid use disorder and psychiatric diagnoses, exclusions from participation in trials among those with prior substance use disorders, and low dose/short duration of opioid exposure. In the circumstances that randomized controlled trials were not available, rigorous, or

applicable to the question at hand (e.g. risk of opioid use disorders among those prescribed opioids), I considered meta-analysis and systematic reviews to be high levels of evidence, and cite them as well as discuss their findings when they are available. Systematic reviews and meta-analysis are considered high levels of evidence because they quantitatively and qualitatively assess the overall body of the literature and provide quality assessments that weight evidence based on reproducible standards. I consider studies that had prospective follow-up of patients or participants, a well-described strategy for statistical control of confounders, and well-designed comparison groups to be the next level of evidence. Prospective follow-up is an important study design because it reduces biases in epidemiological studies from retrospective reporting of symptoms or events. Further, statistical controls are necessary to overcome the potential for bias from confounding. Prospective studies often involve comparison groups (e.g. prescription opioid users and a comparison group of non-prescription opioid users). Study designs with comparison groups provide evidence regarding opioid-related harm that is over and above harm in patient and general population samples across varying levels of opioid exposure. Studies of patient populations without comparison groups, however, are additionally informative particularly for research questions germane to the prevalence of opioid use disorders and related harm among patients prescribed opioids, especially high doses in long duration, as well as questions related to the proportion of drug users who previously used prescription opioids. Well-designed studies of single populations without explicit comparison groups are thus also considered as relevant evidence for characterization of prescription opioid-related harms.

With regard to studies that assess trends over time, I considered three data sources to be the highest levels of evidence. First, I relied on death records that are collected and harmonized by the national vital statistics surveillance system. While death records can have misclassification of causes of death, they are considered by experts to be a reliable indicator of national and local burden of specific causes of death, especially when examining trends over time. Second, I relied on data sources with national reputation for transparency in reliability and validity that assess hospitalization and other clinical records, such as large electronic health databases. Again, while hospital records can include misclassification, data sources gathered from reputable organizations such as the Agency for Healthcare Research and Quality include reliability and validity assessments that allow the researcher using them to be able to draw conclusions based on the best available evidence. Third, I relied on survey data that is routinely collected in the general population of households in the United States over time. Surveys are essential parts of surveillance, given that many cases of substance use disorder do not come to clinical attention, and thus relying on clinically ascertained records can give a biased assessment of trends and burden in the population. Survey data source methodology is to do clustered sampling so that samples are representative of the entire US, and respondents are interviewed with validated instruments that are designed to elicit diagnoses and information with maximum accuracy in the survey context. Generally, I do not include surveys that are not representative of the population or based on samples, as they are not strong evidence for an assessment of the total burden and trends over time.

IV. Detailed Statement of Opinions

B.1. Distribution, sales, and marketing of opioids increased in the 1990s.

There is voluminous evidence regarding the distribution, sales, and marketing of opioids beginning in the 1990s. This evidence is the subject of other witnesses' reports, and I will not repeat all of that evidence here. Instead, I will summarize some points for context. Opioid pain relievers became an increasingly widely-used option starting in the early 1990s, particularly for chronic non-cancer pain, a use that had rarely been seen previously. Estimates from the Automation of Reports and Consolidated Orders System (ARCOS), which tracks prescription distribution and sales, indicate that prescription opioids were dispensed at a range of 96 mg per person in 1997, and increased to 700 mg per person by 2007 (>600% increase).[11,12] . In 1995, the year OxyContin entered the market, the number of prescriptions filled in the US increased by 8 million, and continued to increase over the next two decades before peaking in the fourth quarter of 2010 at 62 million prescriptions dispensed.[13,14] From 1997 to 2002, prescriptions for OxyContin for non-cancer pain increased from approximately 670 000 in 1997 to about 6.2 million in 2002 (prescriptions for cancer pain also increased, about four-fold, across the same period).[15] The supply of opioids was driven by a multitude of

factors, including direct marketing to physicians using data that underestimated opioid use diosrder risks in patients, which I will detail in Section B.2. Evidence shows that pharmaceutical marketing of prescription drugs increases prescribers' likelihood of prescribing the marketed drug in the future,[16,17] including prescription opioids, and resulted in increased sales of the marketed drugs.

Based on this evidence, the rapid increase in total opioid prescribing levels after the introduction of OxyContin in 1996 was driven by marketing and sales of opioids to physicans due to downplaying risks of harms associated with prescribing, including opioid use disorder and overdose.

Evidence published in 2019 indicates that the supply of opioids through prescriptions shows some evidence of decline in recent years, and yet the supply remains high in volume, and significantly higher than it was in the mid 1990s. Data from outpatient prescribing records from IQVIA Xponent database, covering 59,400 pharmacies (representing 92% of retail prescriptions dispensed in the US) examined trends from 2006 through 2017 in milligrams of prescribed opioids, duration per prescription, high doseage prescription fills (>= 90 MME/day), prescriptions filled for 3 days or fewer and 30 days or longer, and extended-released/long-acting formulation prescriptions. While there are overall declines in opioid prescribing, and high dose prescribing, the supply of opioids remains high in volume and prescription length continues to increase. Opioid prescriptions per person in the total US increased annually at an average rate of 6.9% per year until 2010, and decreased at an average rate of 3.8% per year from 2010 through 2015. In 2017, there remained a high level of opioid prescribing in the US, with 191,218,266 prescriptions dispensed, leading authors to conclude that still in 2017 "pharmacies filled enough opioid prescriptions to theoretically provide every US resident with 5 mg of hydrocodone bitartrate every 4 hours around the clock for 3 weeks." Hydrocodone bitartrate has several formulations, including hydrocodone bitartrate with acetaminophen commonly known as Vicodin. Focusing on Ohio in particular, trends mirror the national averages, although there is evidence of a stronger decline in Ohio compared to the national average in recent years. In particular, MME per person increased in Ohio by an average of 6.1% per year from 2006 through 2010; decreased on average by 6.7% per year from 2010 through 2015, and decreased 12.7% per year from 2015 through 2017. Duration per prescription has increased in Ohio throughout the period of 2006 through 2017 (12.4 days in 2006 to 19.3 days in 2017), at an average rate of 4.1 % increase per year.

B.2. Risks of opioid use disorder following medical use of prescription opioids follow a "dose-response" pattern

Early studies cited in marketing materials to physicians underestimated the addiction potential of prescription opioids, and included claims that risks of opioid use disorders are rare among those prescribed opioids. Much of the material provided to physicians on the risks of opioid use disorders after medical prescription of opioids, however, was based on studies that were inadequate epidemiologically, such as Porter and Jick (1980),[18] which did not examine risk of use disorder or dependence based on dose or length of use of opioids, and did not use validated or objective assessments of opioid use disorder. Further, the doses, conditions, and range of medications actually provided to patients often differed from what was cited in these studies. Since early reports, the accumulated evidence regarding the risks of opioid use disorder suggest that the prevalence of opioid use disorder following medical use of prescription opioids is higher than cited in pharmaceutical materials, that the risk escalates with increasing dose, and that both new and recurrent opioid use disorders have higher risk than baseline following a medical prescription.

For this report I reviewed six systematic reviews and/or meta-analyses that assessed opioid use disorder among medical users of opioids.

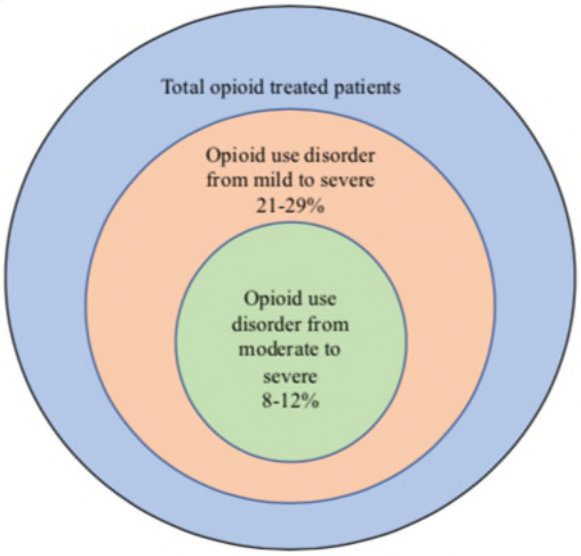
Vowles et al. (2015)[19] provides the most transparent and high-quality review of the evidence of opioid use disorder among patients prescribed opioids for chronic pain. Vowles et al. (2015), unlike other reviews, calculated estimates of prevalence of three outcomes: (1) misuse, described by Vowles et al. as using opioids contrary to directed or prescribed; (2) abuse, described as intentional use of opioids for euphoric effects; (3)

addiction, described as continued use with experience of, or demonstrated potential for, harm. Among studies reviewed, 38 studies met inclusion criteria, which is more comprehensive than comparable reviews also discussed in this report. I will focus on those studies that estimate of opioid "misuse" and opioid "addiction". Given that the measurement of opioid misuse includes criteria of opioid use disorder (use more than intended or prescribed; difficulties with repsonsibilities as to work, school, appointments, etc), the most reasonable analysis of the Vowles study in relation to DSM-V criteria is that Vowles' 8-12% "addiction" rate corresponds to moderate-to-severe OUD, and Vowles' 21-29% category of "misuse" includes the full spectrum of DSM-V categories, from mild (defined as 2-4 criteria met) to severe OUD (8+ criteria met). [20] These studies measured addiction with a range of assessment tools, including diagnostic interviews and urine toxicology. Given that a higher threshold was indicated for "addiction" versus "misuse", the disorders assessed as "addiction" in the Vowles et al. (2015) review generally correspond to opioid use disorders that range from moderate (5-7 symptoms) to severe (8+ symptoms). The highest rates of addiction in Vowles et al. (2015) were documented by Jamison et al. (2010),[21] a sample of over 600 patient that were taking long-term prescribed opioids for non-cancer pain. Individuals in the study completed a series of questionnaires to measure opioid misuse, including patient and provider questionnaires, as well as urine toxicology tests. Opioid use disorder assessments were based on patients scoring above cut-points on the self-reported scale, and in the case that patients were below the cut-off, criteria for opioid use disorder were also considered to be met if the patient scored above a cut-point on the physician-reported aberrant behavior scale and the urine toxicology was positive for an illicit substance or an additional opioid medication that was not prescribed. Individuals in the study had been using opioids for an average of 5-6 years; 34.1% of the sample had evidence of opioid use disorder, including 31% of men and 36.7% of women, indicating a high level of opioid use disorders when patients are assessed with validated instruments as well as objective measures of the presence of opioids such as urine toxicology. The study with the lowest reported rate of opioid use disorder or "addiction" cited in Vowles et al. (2015) was Edlund et al. (2007),[22] based on estimates from a nationally-representative survey of over 9,000 individuals in the community. Authors used several questions that map on to DSM-IV criteria for opioid use disorder (although did not include all criteria, thus the reported evidence is for symptoms of opioid use disorder). Among those who had received a prescription for an opioid, the prevalence of opioid use disorders symptoms was more than 10 times higher than those who had not, at an estimated 7.3%,[2] which is in line with other literature on the range of addiction estimates among medical users of opioids. Controlling for a range of confounders, Edlund et al. (2007) documented that those who used prescription opioids had 3.07 times higher risk of opioid misuse, and 6.11 times higher rates of "addiction". These risk ratios were higher than for other known risk factors for substance use disorders such as mental health diagnoses. Further, the risk of "non-opioid illegal drug use" was not higher among prescription opioid users, suggesting specificity in the relationship between prescription opioid use, and subsequent opioid-related harms. It is important to note, however, that assessments of opioid use disorder based on questionnaires may be an underestimate due to patient reluctance to admit non-medical or aberrant drug use, and that urine toxicology may also be an underestimate because non-medical or aberrant use of prescribed opioid medications may not appear as aberrant on a urine toxicology.

Another way to examine the studies in the Vowles review is to focus on those that are among the highest quality studies. Studies in Vowles et al. (2015) were rated based on the quality of the evidence, as assessed by sampling and data quality, adequate description of methods, and potential influence of the raters on the identification of opioid misuse and addiction. Among these studies, the prevalence estimates of addiction vary but generally are in the range of at least 5-15%. Cowan et al. (2003) reported a rate of "addiction" of 2.8% in a sample of 104 pain clinic patients in the UK who were prescribed opioids – although the authors did not

[2] It should be noted that the Vowles data synthesis mis-cited the Edlund 2007 article by using the "0.7%" rate in the "Addiction" column of Table 5. Close reading of the Edlund text indicates that the 0.7% incidence in the article applied to the entire database, the vast majority of whom had no evidence of having used opioids. Since the other data points in the Vowles analysis were taken from populations that had all been exposed to prescription opioids, that should have been the source for the Edlund data set as well. The 7.3% incidence rate is found in the Edlund (2007) study, based upon the correct population of opioid-exposed individuals.

Figure 1. Estimates of misuse, abuse, and addiction of opioids among chronic pain patients



* Estimated from a systematic review of 38 studies published by Vowles et al. (2015)

assess "addiction" based on DSM or ICD criteria, but instead on their own assessment of maladaptive consequences of use which did not include well-validated criteria such as tolerance and physical dependence. However, it should be noted that 59 of the 104 patients dropped out of the study before study completion. The rate of "addiction" – using the authors' definition – among those who remained in the study was more than double what was reported in the abstract, at 6.5%. Further, this is likely an underestimate given that well-validated symptoms of opioid use disorder were not included in the definition. The highest rates of opioid use disorder, assessed based on a questionnaire that included some DSM substance use disorder symptoms,[23] was 15.7% in a pain clinic sample of 197 patients whose charts were reviewed.[24] The summary of the evidence presented by Vowles et al. (2015) is that among chronic pain patients, an estimated 21-29% of patients meet criteria that would be characterized as between mild to severe opioid use disorder, and an estimated 8-12% of patients meet criteria that would be consistent with moderate to severe opioid use disorders. This summary is included as Figure 1 of this report.

The studies in Vowles et al. (2015) overlap, though not completely, with other reviews of the topic of opioid use disorders after medical prescription.

Fishbain et al. (2008)[25] reviewed 24 studies with various definitions of "addiction" to report an average prevalence of "addiction" of 3.3%, with a range of 0 to 45%; however, there are three central limitations to the Fishbain et al. (2008) review that together suggest that the prevalence of addiction was underestimated. First, authors assessed "aberrant drug-related behaviors" as a marker for opioid use disorder, and studies with low prevalence of aberrant drug-related behaviors were based on designs that did not allow for comprehensive assessment of addiction. For example, Appendix 1 of Fishbain et al. (2008) includes data from 23 studies that assessed aberrant drug-related behavior as assessed by clinical opinion. Of the 5 studies that reported 0% prevalence of addiction, 2 excluded anyone with a current or former history of drug use disorders, and one defined addiction as physical dependence rather than on recommended opioid use disorder nosologies. In contrast, five studies in the review assessed aberrant drug-related behavior based on opioids other than prescribed in urine, or no opioids in urine; the range of prevalences for some indicator of aberrant drug-related behavior was 13% to 40%. Five other studies assessed illicit drugs in urine and found prevalence ranges of 1.1% prevalence of cocaine use through 57% prevalence of cannabinoids or cocaine. In summary, low prevalence of estimated "addiction" are documented in the review when using measures of addiction that are known to underestimate prevalence (e.g. clinical opinion); measures such as urine toxicology find higher rates of addiction. Second, Fishbain et al. (2008) included an assessment of levels of evidence, from the highest levels (meta-analysis of multiple well-designed controlled studies) through the lowest (case reports and clinical examples). Of studies reporting aberrant drug-related behaviors, there were no studies that were rated as the highest levels of evidence. Authors rated each study based on a series of 23 criteria that assessed quality that could be converted into a total score from 0-100. While studies below 50 were considered "low quality", the authors used a cut-off of 65 for inclusion in the review though no validity assessement was done regarding the cut-off score, which omitted several studies that have been included in previous reviews that reported prevalence of addiction from 16-19%.[26–28] Indeed, these omitted studies were

included in a previous review by the same authors (Fishbain et al. in 1992),[29] reporting a higher rate of prevalence of opioid use disorders following medical use, from approximately 3 to 18.9%. Finally, the lead author was a ligitation expert witnesss for Purdue Pharmaceuticals, which was not disclosed in the literature review. Purdue Pharmaceuticals had an interest in publishing studies that underestimated rates of addiction and opioid use disorder among patients prescribed their opioids; thus, the authors have a clear conflict of interest.

Hojsted & Sjogren (2007) reviewed 36 studies focused on individuals with chronic non-malignant pain and with cancer pain, and found a range in prevalence of opioid use disorders from 0-50% among non-cancer pain patients, and 0-7.7% among cancer pain patients.[30] However, the wide range of definitions that were considered as part of "misuse" in the narrative review made for a vague summary of potential rates of harm, and as such the review is of little clinical and public health relevance.

Noble et al. (2010)[31] conducted a systematic review of 10 bibliographic databases through May 2009 assessing opioid use disorder among patients prescribed opioids for chronic noncancer pain after at least 6 months of treatment. In total, 26 studies met inclusion criteria. Investigators reported that the rate of "addiction" was 0.27%, which for several reasons is not a credible estimate for the general patient population receiving opioids. First, of the 27 treatment groups assessed in the 26 studies, 18 excluded individuals with any history of substance use disorders from participation, and the remaining 9 did not state whether patients with a history of substance use disorders were excluded or not. Further, 18 studies did not assess opioid use disorders as an outcome, and thus they are not relevant to the question of opioid use disorder risk among patients. Among the 2,613 patients included in the review as having been assessed for addiction potential, and Noble etl a. inappropriately concludes that addiction is rare based on a calculated "event rate" 0.27%. Among the 7 studies that reported addiction among patients, 2 reported non-zero cases, for a total of 7 cases. A closer look at the 2 studies that were used to comprise these 7 cases reveals the flawed methodology for this event rate estimate. Portenoy et al. (2007),[32] in a study sponsored by Purdue Pharma, reported "problematic drug-related behavior" in 13 patients among 227 who were treated with controlled-release Oxycodone for 1-3 years, for an incidence of 5.7%; an expert review panel of those 13 patients concluded that 6 had probable opioid use disorder. Problematic drug-related behaviors included symptoms of drug use disorder, seeking prescriptions from other doctors, withdrawal symptoms upon discontinuation of medication (although no other criteira for opioid use disorder was used), and other patients with suspected symptoms of opioid use disorder but without definitive evidence for a diagnosis. These reports are likely an underestimate, given that urine toxicology was not performed, and that patients receiving opioids under-report opioid use disorder symptoms. Further, the sponsorship of the study by Purdue Pharma suggests that there was a financial interest in reporting a low number of opioid use disorders in the patient population, suggestive of bias due to financial conflicts of interest. The other study cited by Noble et al. (2010) as evidence for low risk of opioid use disorders was Anderson et al. (1999),[33] a study of 30 individuals prescribed intraspinal morphine and followed for 24 months on average. One patient among the 30 was described as having "drug-seeking behavior", and was thus included in the Noble et al. (2010) review as a case of addiction. However, it should be noted that within this 30 person trial, 3 persons died and 5 more had only partial follow-up data; the remainer were not systematically assessed for opioid use disorder. Thus the actual event rate is unknown. To infer an event rate of 0.27% based on 7 cases reported in 257 patients, many of whom were not systematically assessed for opioid use disorder or assessed with urine toxicology, based predominantly on one industry-funded study, is inappropriate and not scientificially rigorous.

Minozzi et al. (2012) reviewed 17 studies involving 88,235 patients that subsumed systematic reviews, one randomized trial, eight cross-sectional studies and four case series. The majority of studies included patients with non-cancer chronic pain who had been treated with opioids for long periods of time. Recorded incidence of opioid use disorders across these studies ranged from 0 to 24%, and prevalence ranged from 0 to 31%. However, again, many of the studies assessing non-medical opioid use, and opioid use disorders, among medical users likely had underreporting and undercounting of opioid use disorder symptoms, as they were based primarily on chart review rather than structured diagnostic interviews and/or urine toxicology.

Finally, Martell et al (2007)[34] focused on patient populations with chronic back pain. The authors reviewed 4 studies that reported prevalence rates of aberrant drug using behavior which ranged from between 3 and 43%, which is in line with the review by Vowles et al., which focused on a broader patient population but had prevalence estimates of addiction in the same range. Further Martell et al. (2007) also included analysis of 5 studies that reported substance use disorders, which were reported by approximately 36% to 56% of patients included in the studies.

In summary, the range of reviews available on the risks of "misuse" and "addiction" of prescription opioids from medical use vary because of differences in inclusion criteria and definitions. However, the results of multiple studies with a wide range of designs indicate that risks are high when opioids are prescribed in large doses for long periods of time, with available and reliable estimates indicating that opioid misuse rates range from 21-29% (corresponding to opioid use disorder ranging from mild to severe), and that opioid addiction risk among this group ranges from approximately 8-12% (corresponding to opioid use disorder ranging from moderate to severe), with even higher rates when assessing individuals who are on high doses of opioids for long periods of time.

More recent studies that were not included in aforementioned reviews also provide evidence that risks of opioid use disorders are substantial after medical use. Using a large pharmacy and medical claims database from 2000 to 2005, Edlund et al. (2014) documented that the risk of chart-documented opioid use disorders increased with both dose and duration of opioid use in a large health services database of adults[35] The majority of the sample were either non-opioid users (65% of the sample), or those who had been prescribed opioids for acute pain at low doses (94.1% of those prescribed opioids). Among those who had high dose opioids for a greater number of days, the risk of opioid use disorders was in line with what previous reviews and meta-analyses suggest is the range of prevalence esitmates for opioid use disorders among medical users, at 6.1% incidence of new opioid use disorder. The level of risk of incident opioid use disorder varied according with the dose and length of opioid use, and there was a dose-response relationship between dose and length of opioid use and incident opioid use disorder diagnosis including high daily dose (≥100 MME), and long-term opioid use (>3 months), with highest risk of opioid use disorders observed among persons prescribed high doses (≥120 MME) for long-term use (91+ days). Indeed, among these patients, the risk of incident opioid use disorders was 122.5 times higher than those with no opioid use, after adjustment for age, sex, indicators of pain and mental disorders, and the estimated incidence was around 6% for these individuals. But even at very low levels of use, the risk of opioid use disorder diagnoses was significant. Among those with acute (1-90 days of use) opioid use at a low dose (1-36 MME), risk of incident opioid use disorders was 3.03 times higher than those with no opioid use. There is also undercounting of opioid use disorders using clinical records. Edlund et al. (2014) relied on incident diagnoses with a relatively short window after opioids use, which would not capture those with recurrent opioid use disorder symptoms or those who did not develop symptoms shortly after use. Thus, total burden is likely underestimated, and may be considered a lower bound of all potential harm. Of note, as summarized in the definitions section of this report, opioid use disorder diagnoses are over and above the expected physical dependence on opioids that can occur during medically supervised use (tolerance and withdrawal). Such symptoms would be anticipated based on prolonged use of opioids that were taken for medical reasons; in contrast, opioid use disorders include tolerance and withdrawal and are indicators of impaired control over opioids.

Finally, Boscarino et al. (2015)[36] utilized data on patients randomly selected from outpatient clinical records who were receiving care for non-cancer conditions such as pain, arthritis, and orthopedic conditions and had been prescribed five or more prescription opioid medications in a 12 month period. Patients consented to structured interviews for opioid use disorder based on DSM-IV and DSM-5 criteria (N=705). Among these patients, 28.1% had 2-3 symptoms of opioid use disorder (designated in DSM-5 as "mild" disorder), 9.7% had 4-5 symptoms ("moderate" disorder), and 3.5% had 6+ symptoms ("severe" disorder), for a total prevalence of any opioid use disorder from mild to severe of 41.3%. These rates are remarkably consistent with Vowles et al. (2015), in that the prevalence of "addiction" was estimated between 8-12%, which is

consistent with the total of moderate and severe opioid use disorder reported by Boscarino et al., in that moderate and severe opioid use disorder together would be an estimated 13.2%. Futher, Vowles et al. (2015) estimated that the prevalence of opioid "misuse" was between 21-29%, which is consistent with the 28.1% prevalence from Boscarino et al. for "mild" opioid use disorder. Such evidence of consistency provides additional support for the reliability of the results.

Risks of opioid use disorder after prescription opioid use are not solely determined by dose and length of opioid use. Individual risk-factors for opioid use disorders include younger age (e.g., 18-30), lifetime history of psychoactive illicit drug use, and lifetime psychiatric or substance use disorder. However, risks for opioid use disorder based on dose and length of opioid prescription persist even when controlling for these risk factors, and the magnitude of the association for dose and duration of opioid use are greater than individual-level risk factors for opioid use disorders, even when taking them all into consideration together. Nevertheless, the burden of opioid use disorders following medical prescription of opioids, especially at high doses and for long duration, is especially greater among those who already have vulnerabilities to addiction. Indeed, results of studies that exclude those with a history of drug use disorders from inclusion in the study sample are not generalizable to the total patient population of individuals receiving opioid medication therapies due to the higher baseline risk for addiction.

Generally, the existing evidence likely underestimates the total burden of opioid use disorders. Even in the setting of high-quality evidence and structured diagnostic interviews with adjunctive evidence through urine toxiology, existing studies routinely underestimate opioid use disorder. Less than half of substance use disorders identified in community samples are even diagnosed and/or treated in medical settings, and thus a substantial portion, upwards of half, of total diagnoses are likely missed throughout studies that recruit and treat patients in medical settings. Further, studies using urine toxicology screens, validated instruments for opioid use disorder, and other high-quality objective indicators demonstrate a higher proportion of opioid use disorder than studies relying on administrative records that are not collected for research purposes.[37,38] Studies that use diagnostic questionnaires provide assessment of opioid use disorder that are more valid than case files, though may still underestimate rates of opioid use disorder, especially in medical settings where patients may not want to disclose problems related to medication useage. Diagnostic interviews coupled with urine toxicology identify more cases than either alone. For example, Katz et al. documented that 21% of patients with no behavioral symptoms of substance use disorder had positive urine screens for illicit drugs or nonprescribed controlled medication, and 14% of those without positive urine toxicology had evidence of substance use disorders in a sample of 122 patients maintained on long-term opioids for noncancer pain.[39] Additional studies have also provided evidence that urine toxicology identifies individuals with drug use disorders among those who deny such use in interviews among medical opioid users,[37] suggesting that the combination of urine toxicology plus structured, valididated self-report measures, together provide rigorous data to assess drug use disorders among medical users of opioids.

In summary, there is a wide range of reported prevalence and incident estimates of opioid use disorders among patients. The reasons for this range include the characteristics of the samples (e.g. pain conditions, amount and types of opioids used, individual-level patient characteristics that predispose individuals to developing opioid use disorder) as well as the measurement of opioid use disorder, sample size and study design. However, the high-quality evidence across reviews indicates that the risk of incident opioid use disorders, as well as recurrence of opioid use disorders, increase in a dose-response fashion with the dose of opioids and the length of opioid use, even after controlling for individual-level predisposing factors. Importantly, the evidence is clear that risks of opioid use disorder following medical use of prescription opioids follow a "dose-response" pattern.

B.3. Opioids were diverted and used by individuals with opioid use disorder and for non-medical use

In Section B.2. I reviewed the evidence for opioid use disorders after medical use of opioids, however an additional consequence of the increased supply of opioids was also opioid diversion. That is, the evidence shows that prescription opioids are diverted from the supply chain from medical facilities and pharmacies for

sale to the black market for distribution and sale for non-medical uses, and that this non-medical use of opioids, stemming from diversion, has also contributed to harm. It is important to note that this discussion of diversion isolates one contributing factor; it does not speak to an important precursor—the fact that individuals who develop opioid use disorder after receiving an opioid prescription, will be compelled to seek other sources of opioids, including prescription opioids. This will include prescriptions obtained by friends and families, from multiple doctors, or from high volume prescribers. This is not a independent cause of the harm, but a result related to the overprescribing and oversupply of opioids described above.

Data on the diversion of opioids are drawn from a variety of sources;[40] all data sources have found that prescription opioid diversion is common, especially unused prescriptions that were overprescribed to friends and family members of the non-medical users. Given that close to 98 million Americans receive prescription pain relievers every year, a much larger number than the estimated 12.5 million who use opioid non-medically,[2] the contribution of diversion through sources such as family and friends for non-medical use is a small proportion of the overall expansion in the opioid supply and resultant opioid-related harm. Data from the National Household Survey on Drug use and Health from 2013-2014 indicates that among non-medical opioid users interviewed about where they obtain their opioids, 50.5% report from a friend or relative.[41] Other data sources on drug diversion converge in supporting the fact that the common routes for opioid prescriptions on the illicit marketplace are drug dealers as well as family and friends. Inciardi et al. (2009)[42] reviewed a number of studies that estimated illicit sources of prescription opioids. Data from the NSDUH, a national sample from households in the general population, show that 57% of non-medical opioid users in 2007 obtained opioids from a friend or relative for free, with another 9% reporting that friend or relative for purchase was also a source of opioids. Of those reporting their source as a friend or family member, approximately 80% of these friends or family members are reported to have received opioids from a single prescriber. In contrast to users in treatment, a relatively small proportion of individuals in the NSDUH obtained opioids from a dealer. Data sources focused on adolescents and young adults support these findings; a large survey of college students found that peers and family were the most common sources of prescription opioids.[43,44]

Medical sources of prescription opioids that are used for diversion and non-medical use are also common, and confirm the link between opioid use disorder and misuse of opioids, Shei et al (2015)[45] analyzed data among 9,291 commercially insured patients aged 12-64 who had a recorded diagnosis of opioid abuse or dependence, and 395,901 comparison individuals with no diagnosis. To estimate diversion, authors examined the proportion of patients who had a prescription for opioids in their prescription record prior to their opioid abuse/dependence diagnosis. Authors also examined the proportion who had a family member with an opioid prescription claim prior to the abuse/dependence diagnosis, using a family member linkage identification key. Among those with opioid abuse/dependence, 79.9% had at least one claim for a prescription opioid prior to diagnosis, compared with 56.8% of patients with no diagnosis of opioid abuse/dependence. Further, 50.8% had a family member with an opioid prescription claim, compared with 42.2% of patients with no diagnosis; 20.1% of those with an opioid abuse/dependence diagnosis had no record of a prescription opioid, indicating that opioids were obtained through diverted sources. Individuals who have become addicted to and/or misuse opioids are likely to seek to obtain them from any available source, including doctors. Data from the NSDUH from 2013-2014 indicate that while family/relative is the most common source of non-medical prescription opioids, 25.1% obtain opioids from one or more physicians.[41] Among the various samples of users reported by Cicero and colleagues (2011),[46] medical sources of prescription opioids were commonly reported. For example, among 1,983 individuals in treatment for opioid dependence, 25% reported that their primary method of obtaining access was through doctors, and more than 50% reported that doctors were among the various methods of obtaining opioids. Among the sample of 782 individuals in substance abuse treatment collected in South Florida, 13.8% reported obtaining opioids from a medical practice (however, it should be noted that these results were assessed prior to the restrictions on high-volume prescribing in Florida, thus may not be generalizable to more recent years).[46] Doctors and other sources of obtaining prescription opioids were more common among those whose primary drug of abuse is a drug more commonly prescribed (hydrocodone) and less common among those

whose primary drug of abuse was OxyContin. In a study of 346 individuals with prescription opioids as a primary drug of abuse and in methadone maintenance, 20% reported doctors as a primary source, and 9% reported emergency rooms.[42] Data from the NSDUH study indicated that among those who reported non-medical prescription opioid use, 18% reported that they obtained opioids for non-medical use from a doctor.

The diversion of opioids, whatever the source, has been well-established and well-known. Further, studies of law enforcement also support that diversion occurs and is associated with harm. From 2005 to 2009, based on data from the National Drug Threat Survey, the proportion state and local law enforcement agencies surveyed reported diverted pharmaceutical drugs as the greatest drug threat in their communities increased from 3.9% to 9.8%. In 2009, 48% of law enforcement agencies surveyed reported that diverted pharmaceutical drugs were associated with street gang involvement, and 8.4% and 4.8% reported that diverted pharmaceutical drugs were causes of property and violent crime, respectively.[47]

A small proportion of individuals using opioids chronically receive prescriptions from multiple prescribers and pharmacies, and have been characterized as "doctor shoppers" or "opioid shoppers". McDonald & Carlson (2014)[48] documented drug diversion through "doctor shopping", documenting that it is associated with the overall prevalence of opioid prescribing (supporting the conclusion that availability and access facilitate doctor shopping), but that overall it remained rare across states with a mean of 0.7 per 1,000 individuals across states. Similarly, with respect to diversion, a small number of rogue prescribers have operated in "Pill Mills" that have accounted for the prescribing and dispensing of disproportionately large volumes of opioids. These Pill Mills, and the "rogue prescribers" who have operated them, have been subject to local law enforcement actions as well as state laws to prohibit them. Available data indicate that prescribing of opioids increased across many specialties in medicine, and while some specialties of medicine have a more concentrated prescription practice for opioids (e.g., pain, anesthesia, and physical therapy), general practitioners in family and internal medicine dispenses the greater number of opioids, widespread across geographic areas of the US.[49] This indicates that opioid prescriptions increased across many sectors, and across clinical practice areas. As such, 'Pill Mills' do not explain in any significant way the expansion of opioid prescribing and opioid-related harm in the US.

In summary, diversion of opioids has been fueled by their oversupply, occurs all along the supply chain, and is especially problematic and well documented among end-users – that is, among individuals with non-medical use or OUD who report that friends or family members serve as a source of their opioids. Licensed prescribers are also common sources of opioids used non-medically.

B.4. The incidence and prevalence of non-medical opioid use increased in concert with the increased supply of opioids

The evidence is clear that the opioid supply increased dramatically in the United States beginning in the early 1990s, that medical use of opioids is associated with the development of opioid use disorder, and that diversion of opioids to the illicit market occurred. An additional consequence of the increased supply of opioids was an increase in the incidence and prevalence of non-medical opioid use and non-medical opioid use disorder in the general population, due to the oversupply of opioids. Evidence regarding non-medical prescription opioid use in the general population is not generally available as early as 1999 for adults. Among adolescents, data can be drawn from the Monitoring the Future study, a large, annually conducted survey of high-school attending adolescents. Among students in the 12th grade, for example, use of "narcotics other than heroin" increased annually beginning in 1992, from 3.3% to a peak of 7.0% in 2000. In 2002, the question wording and example changed, thus trends before and after 2002 cannot be directly compared. McCabe et al. reported these trends in prevalence in both medical and nonmedical use in a 2017 publication in *Pediatrics*, noting that adolescent non-medical use of opioids is frequently preceded by medical use in the adolescent population.[50] The prevalence of narcotics other than heroin has been generally declining among adolescents since the early 2000s.[51]

While prescription opioid use has been declining among adolescents, among adults, trends indicate that prescription opioid use is stable, with generally low magnitude declines since 2012 but still a high burden of harm for heavy use and addiction. Martins et al. (2010) documented birth-cohort trends in non-medical prescription opioid use and opioid use disorder by comparing two surveys: one conducted in 1991-1992, and another, using the same sampling frame and measurement questions, in 2001-2002. The study found that among adults, past-year non-medical prescription opioid use increased by 44% (from 0.9 to 1.3%) across the decade, and that past year prescription opioid use disorder increased by 55% (from 0.2 to 0.3%). Among those who reported non-medical prescription opioid use in their lifetime, the prevalence of past-year opioid use disorder increased 89.6% (from 4.8 to 9.1%).[52]

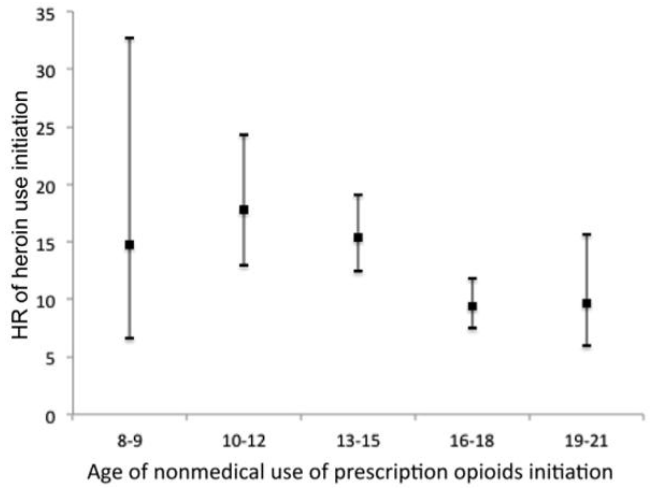
Other data can be drawn from to infer trends in non-medical prescription opioid use during the 1990s and 2000s. Crane (2015), for example, documented that emergency department visits for non-medical prescription opioids use from 2005 to 2009 increased over 200 percent among those aged 18-34 years old, a greater increase than any other age group.[53] Analyses of the Drug Abuse Warning Network data have found increases in ED mentions of opioid analgesic misuse through 2011; for example, the number of ED mentions of oxycodone increased from 41,701 in 2004 to 151,218 in 2011. Total for all pharmaceutical opioids, ED mentions increased from 152,827 in 2004 to 404, 829 in 2011.[54] Finally, data from the Treatment Episode Data Set indicate that from 2005 to 2015, the proportion of individuals entering treatment with prescription opioid use as the principal drug for services increased from 18% to approximately 38%.[55]

More recent trends generally observe that the prevalence of non-medical prescription opioid use is stabilizing or beginning to decline, depending on the population and outcome, but that burden remains substantial. For example, data from the NSDUH indicate that among those 18 through 64, the prevalence of non-medical prescription opioid use decreased from 5.4% in 2003 to 4.9% in 2013. However, the same study documented that harms related to opioid use remained on the rise, with increased prescription opioid use disorders, frequency of use, and mortality (mortality will be reviewed in detail in Section B.5.).[56] Indeed, from 2003 through 2013, the prevalence of opioid use disorders increased from 0.6% to 0.9%; high frequency use increased from 0.3% to 0.4%. Among users, the prevalence of opioid use disorder increased from 11.9% to 17.8%, and high frequency use increased from 5.0% to 8.2%, and mean days of use increased from 40.0 to 54.2 days. Comorbidity with other drug use disorders ranges from risk ratios of approximately 1.50 to 2.0. Important to consider in interpreting the evidence is limitations of survey data sources, which consistently underestimate the populations at highest risk of opioid-related harm. Existing survey data sources capture rates of non-medical opioid use and opioid use disorder among those living in households and group quarters as the explicit sampling frame. Such surveys do not include high risk populations such as those incarcerated and homeless. Existing research demonstrates that survey responders are generally healthier than the general population,[57] and thus fewer individuals using opioids non-medically and those with opioid use disorder will be captured in these data systems compared to the actual burden in the population. Indeed, heavy opioid use is associated with criminal justice involvement and homelessness,[58–60] thus I would expect that those with the highest burden of use would be least likely to be captured in household-based surveys. Nevertheless, while estimates of prevalence are likely underestimated, the trends over time should not be affected as long as underestimation is consistent across time.

Further, survey data sources regularly query explicitly non-medical prescription opioid use, and do not collect information on the portion of respondents who also used opioids medically, either prior to or concurrently with non-medical prescription opioid use. However, data indicate that a substantial portion of non-medical users obtain opioids at some point from physicians for medical uses (see Section B.3. for discussion of and reference to patterns of physican contact among non-medical users).

In summary, the expansion of non-medical prescription opioid use would not have occurred without the widespread availability of prescription opioids that were originally dispensed for medical uses, often in greater quantities and doses than needed, leaving a surplus of opioids that could be diverted for non-medical uses. There is sufficient evidence to conclude that non-medical prescription opioid use, prescription opioid disorder, and ED visits for prescription opioid use increased in the US population from the 1900s through the late 2000s. Available evidence indicates declines in overall non-medical prescription opioid use in recent years among both adolescents and adults, but there remain steady increases in heavy use and opioid use disorders, indicating that the burden of harm remains high.

Figure 2. Fitted hazard ratios of heroin initiation associated with prior nonmedical prescription opioid use, by age of nonmedical prescription opioid use initiation (NSDUH, 2004-2011)



B.5. The increase in the prescription opioid supply, coupled with opioid use disorders and increases in non-medical use and non-medical opioid use disorder, resulted in an exponential increase in prescription opioid overdose.

Data on the increase in prescription drug overdose deaths in the United States are primarily drawn from the National Vital Statistics Surveillance System. In 2000, the overdose death rate attributed to prescription opioids was 1.4 per 100,000 (representing 4,030 designated deaths). By 2003 the rate had more than doubled to 2.9 per 100,000 (representing 8,517 designated deaths), and the rate continued to increase yearly until approximately 2010 (at a rate of 5.4 per 100,000, representing 16,651 deaths).[61] From 2010 to 2014, the rate remained relatively stable, albeit a quadrupling of the rate that was observed in 1999, after which increases in the overdose death rate renewed. Heroin and synthetic opioids began an exponential increase after 2010, and overdose rates due to heroin and synthetic opioids continue to climb. However, it is important to note that prescription opioid deaths remain an important contributor to overall overdose deaths, even as heroin and synthetic opioid deaths rise exponentially. From 2016 to 2017, I examined the rates of opioid overdose based on two sets of causes of death: (1) all natural, semisynthetic, and methadone opioids; and (2) natural and semisynthetic opioids alone. The rate of natural, semisynthetic category, when including methadone overdose, has remained virtually unchanged, at 5.2 per 100,000 in each year, representing 17,087 deaths in 2016 and 17,029 deaths in 2017.[62] Considering those deaths designated as natural and semisynthetic opioids alone (i.e. excluding methadone deaths), death rates are also consistent from 2016 to 2017, indicating a high burden of harm.[63] In 2016, the death rate for natural and semisyntheic opioids was 4.4 per 100,00 (representing 14,487 deaths), and remained at 4.4 per 100,000 in 2017 (representing 14,495 deaths).

There have been rapid increases in opioid overdose death due to heroin and synthetic opioids, beginning in approximately 2015.[64] While these increases are concerning, it is important to note that they remain overshadowed by the total burden of prescription opioids overdose deaths. Examining the total number of overdose deaths due to natural and semisynthetic opioids, which would exclude heroin and fentanyl deaths, there have been a total of 230,869 deaths since 1999 through 2017. This number of deaths is greater than the deaths from heroin over the same time period (N=100,599) plus the number of deaths due to non-methadone synthetic opioids (N=93,151), combined. There has been virtually no change in the burden of prescripton opioid death in the United States in recent years (N=14,487 deaths in 2016, and N=14,495 deaths in 2017), suggesting that the burden of prescription opioid overdose in the United States remains high,

greater than heroin and synthetic opioids combined over the course of the epidemic, and that the burden is not substantially decreasing, underscoring the public health burden of prescription opioid overdose.

The empirical literature demonstrates an association between the opioid supply and the increase in prescription opioid deaths. Based on retail pharmacy data in two provinces in Canada from 2005 through 2009, Fisher et al. (2013) documented statistically significant and high correlations between the rate of hydromorphone dispensing and deaths due to hydromorphone, as well as the rate of oxycodone dispensing and deaths due to oxycodone. These correlations were high within-province, which is important because the base rates of overdose and dispensing varied by province and yet the correlations remained strong in each. Similar associations with non-fatal outcomes such as substance abuse treatment admissions have been published by the same investigators, indicating that the association between prescription opioid supply and opioid-related harms in Canada extends across outcomes related to opioid use disorder as well as opioid overdose.[65]

In the United States, Paulozzi & Ryan (2006),[66] documented wide variation across US states in the distribution of prescription opioids, based on data from the Automated Reports and Consolidated Orders System (ARCOS). Scholars estimated the total rate of prescription opioid dispensing per 100,000 in each state in 2002, and correlated it across states with the drug poisoning death rate per 100,000 based on vital statistics data. Two findings are noteworthy. First, there was wide variation in opioid prescribing across states. For example, hydrocodone distributions ranged over 12-fold across states, and oxycodone distributions ranged over 7-fold; such variations are noteworthy because to my knowledge there is not sufficient data to conclude that the pain need for such medications varies by 7 to 12-fold across US states. Further, this variation across states was highly correlated with drug poisoning rates; all prescription opioids combined were correlated with drug poisoning deaths at 0.73 for the correlation coefficient, which indicates a high correlation. Investigators reported the total amount of variation, that is, differences between state-level overdose rates and the national average, that was explained by each drug. Note that variance explained is not the same as the risk of overdose, or the proportion of overdose deaths due to a particular drug, rather, it is another way to express correlation. Oxycodone dispensing alone explained 43% of the variation in drug poisoning mortality; methadone dispensing explained 46%. While the death rates from methadone substantially contributed to mortality variation in Paulozzi & Ryan (2006), it should be noted that death rates from methadone have declined precipitously since the time period of the study. Methadone death in the US reached a height in 2006/2007 at 1.8 per 100,000, and had declined annually since then, stabilizing at 1.0 per 100,001 in 2015-2017, [64] which is a 44% decerase in just one decade. Methadone now contributes a relatively small proportion of drug overdose events, with most recent data suggesting that 14.7% of overdose deaths are attrituable to methadone. These declines are attributable to Food and Drug Administration warnings and guidelines for methadone prescribing, as well as voluntary limits on the distribution of high milligram formulations of methadone among manufacturers.[67] Given the declines in methadone use, the findings on methadone in Paulozzi & Ryan (2006) regarding the proportion of variance explained in geographical death rates do not generalize to distributions of opioid related harm in recent years. However, prescription opioid overdose deaths are higher than methadone rates of death and have remained relatively stable in recent years, suggesting that geographic variation explained in prescription opioid overdose deaths is more generalizable than methadone death rates.

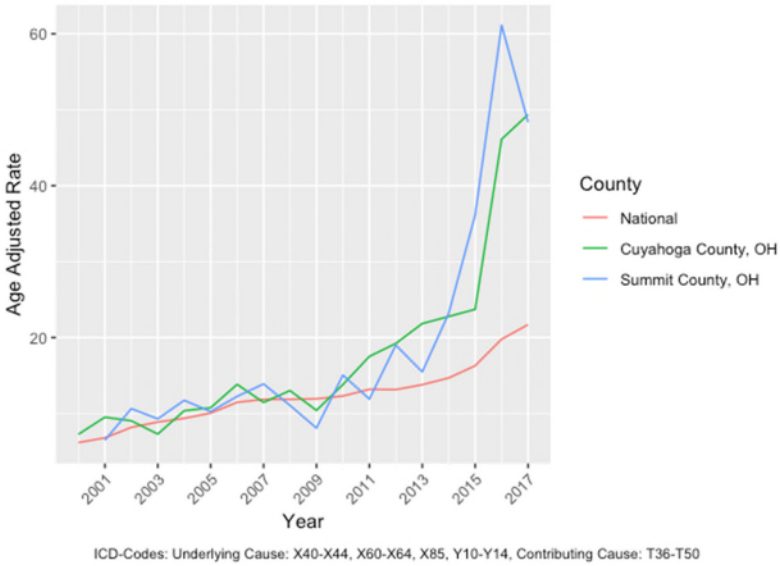
Further, Wisniewski et al. (2008)[68] examined the relationship between prescribing of opioids and non-medical opioid use, as well as emergency department visits related to opioids. Data on prescribing were drawn from the National Hospital Ambulatory Medical Care Survey and the National Ambulatory Medical Care Survey; opioid prescriptions were based on medication codes indicating whether hydrocodone, oxycodone, or a morphine-containing product were prescribed at each patient encounter (including 576,178 patient encounters). Prescription rates increased from 2-fold for hydrocodone, 2.64 for morphine, and 3.21 for oxycodone products from 1995 to 2004. Concomitantly, opioid-related emergency department visits based on DAWN data and respondent reports of non-medical opioid use based on NSDUH data increased across the same time period. Correlations between rates of prescription and rates of opioid-related ED visits and non-medical use were significant for hydrocodone (correlations ranged between 0.73 to 0.79) and oxycodone

(correlations ranged from 0.76 to 0.87). Taken together, these data indicate strong and statistically significant correlations between opioid supply and prescribing practices, and opioid-related harm in the US population.

Pharmaceutical company marketing to physicians, often based on sources that underestimated the risk of opioid use disorder, harm, and diversion, as discussed in Section B.2., contributed to the increase in the supply of opioids.[15] These marketing practices led to consequences for opioid-related harm. Pharmacuetical company marketing to physicans is extensive in the United States.[17] Empirical evidence has demonstrated that industry payments to physicians as part of the marketing of prescription opioids were associated with increased opioid prescriptions,[69] and that 1 in 12 physicians in the US, and 1 in 5 family physicians, received opioid-related marketing.[17,69–71] Hadland et al. (2019)[72] used data form the Centers for Medicare & Medicaid Service Open Payments database to assess the monetary value in payments to physicians for opioid products in all US counties over time, as well as data on dispensing of opioids in available counties in the US, and examined the spatial and temporal correlations with prescription opioid deaths as designed in the vital statistics records. Authors used a rigorous statistical model that included controls for a range of county-level factors such as economic environment (e.g. unemployment, income, income inequality) as well as demographics. Results demonstrated that even with statistical controls in place, each one standard deviation increase in payments to physicians was associated with statistically significant increases in prescription opioid overdose; including when marketing was assessed by marketing value in dollars per capita (each standard deviation increase associated with 1.09 times the rate of death), number of payments to physicians per capita (each standard deviation increase associated with 1.18 times the rate of death), and number of physicians receiving marketing per capita (each standard deviation increase associated with 1.12 times the rate of death). Further, these authors conducted mediation analysis to quantitatively demonstrate that the association between marketing to physicians and prescription opioid overdose was mediated by (that is, explained by) the increase in opioid prescribing and increased distribution. However, it is important to note that payments to physicians are only one type of promotional activity, and accounted for only a proportion of the overall promotion strategy for opioid pharmacueticals. These results are highly rigorous and clearly demonstrate harm to the population from opioid marketing and distribution.

Finally, a working paper authored by Powell et al. (2015)[73] examined the introduction of the Medicare Prescription Drug Benefit (Part D) program in 2006 as a potential driver of the opioid supply among those aged 65+. This paper is particularly relevant given the quasi-experimental design of using an exposure with exogenous variation, and a new law passed heterogeneously across states, to assess changes in the opioid supply. "Exogenous variation" is a term that is commonly used in epidemiological and economics literature to mean that there is no possibility that confounding factors such as increased prevalence of pain, or increased risk factors for addiction, could explain changes in the exposure. Thus, changes in the Medicare system cannot be caused by users of that system, and as such, associations between changes in the Medicare system and changes in opioid supply are more likely to be causal. Using data from 1999 through 2016, authors documented that the Medicare expansion affected the opioid supply, with states that had a relatively larger proportion of individuals gaining access to prescription drug coverage exhibiting an increase in opioid supply based on ARCOS data. Further, authors examined correlations with drug overdose deaths, and specifically those with codes that indicate prescription opioid poisoning, as well as substance abuse treatment admissions, an indicator of the occurrence of opioid use disorders. For both prescription deaths and treatment admissions, there was evidence that the increase in the opioid supply was associated with increases in deaths and treatment admissions; results were robust to a range of sensitivity analyses, alternative modeling of the statistical associations, and a range of quasi-experimental statistical models. As such, these data reinforce the conclusion that the opioid supply directly affects opioid-related harm, and provide a strong design and test of the hypothesis using the quasi-experimental instrument of changes in Medicare prescription coverage.

Figure 3. Overdose death rates, all drugs



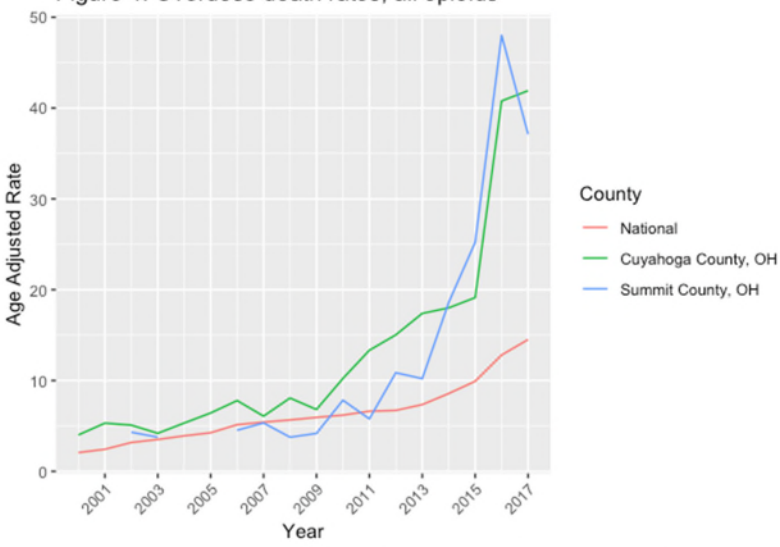
ICD-Codes: Underlying Cause: X40-X44, X60-X64, X85, Y10-Y14, Contributing Cause: T36-T50

In summary, the available evidence, including temporal and geographic covariance of opioid supply as well as quasi-experimental changes in opioid availability, strongly correlate with rates of prescription opioid overdose, providing an evidence base to demonstrate that supply and availability of opioids caused an increase in the rate of prescription opioid overdose.

B.5.1. Opioid-related harm in bellwether counties (Cuyahoga County and Summit counties) has increased greatly between 2000 and the present, and the death rates due to prescription opioids consistently exceed the national average.

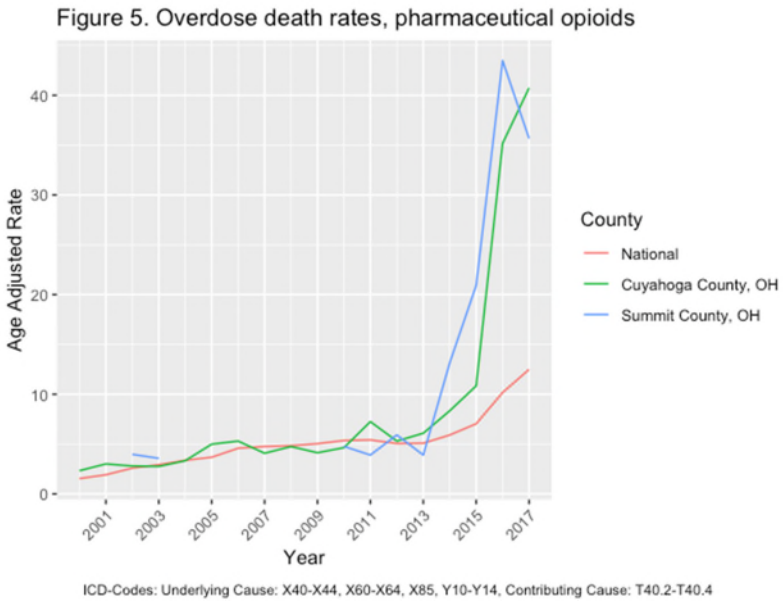
The National Vital Statistics Surveillance System publicly provides county-level data on death, allowing for a quantification of the risk of overdose death. Of particular relevance are trends in opioid-related deaths in Cuyahoga and Summit counties. The death rates from 2000 through 2017 for: drug-related death, opioid-related death, and prescription opioid death from the vital statistics records are shown in Figure 3, Figure 4, and Figure 5. Vital statistics has not yet released rates of drug overdose by county for 2018 and 2019, thus we focus on conclusions through 2017 using the data that has been adjudicated and harmonized through the vital statistics process. However, we report on preliminary data from the counties regarding overdose deaths in 2018 as well, though note that estimates may shift as deaths are harmonized with the vital statistics system.

Figure 4. Overdose death rates, all opioids



ICD-Codes: Underlying Cause: X40-X44, X60-X64, X85, Y10-Y14, Contributing Cause: T40.0-T40.4

These data indicate that rates of overdose death in Cuyahoga and Summit counties have been increasing since 2000. Compared to the national average, pharmaceutical opioid deaths were 1.51 times higher in Cuyahoga County than in the nation as a whole in 2000 (based on 32 deaths in Cuyahoga County); the standardized mortality ratio comparing pharmaceutical opioid deaths in Cuyahoga County to the national average varied across the years from 2000 to 2016, with some years lower than the national average. By 2016, the pharmaceutical opioid death rate in Cuyahoga County was 3.26 times higher than the national average (based on 425 deaths in Cuyahoga County). A recent publication from the medical examiner's office of Cuyahoga County (Gilson et al. 2017)[74] confirms the recent rapid increases in death from opioids within Cuyahoga County; based on the medical examiner data, the total overdose mortality in Cuyahoga County has increased from 250 in 2006 to 608 in 2016. In recent years, heroin and fentanyl deaths have increased more than any other drug cause; with heroin deaths increasing from 184 to



299 from 2015 to 2016, and fentanyl deaths increasing from 92 to 394 from 2015 to 2016 alone. Of note, a large proportion of the the increases in heroin and fentanyl deaths are a result of the increase in prescription opioid use in the United States, given the evidence that prescription opioid use is often the first drug used in the sequence of opioids that result in heroin and fentanyl use. Data from vital statistics are corroborated by data from the Cuyahoga County medical examiner's office,[74] which published that in 2016, there were 299 heroin overdose deaths, 89 other opioid deaths not including fentanyl, and 394 fentanyl deaths. Preliminary data from 2018 in Cuyahoga county indicate 440 opioid-related deaths, down from 556 in 2017. [75] The deaths reported by the medical examiner differ from the deaths reported by vital statistics in that they include all deaths that occurred in the county, not just the deaths of residents of the county, but we can conclude from these preliminary results that opioid-related deaths in Cuyahoga county have demonstrated some decline in the past two years but still remain exponentially higher than levels even a decade ago.

In Summit County, mortality ratios for pharmaceutical opioid deaths could not be compared to the national average in all years because public use files do not include death rates for counties with low population counts and/or low numbers of deaths in order to reduce the potential for confidentiality violations. In 2002, the first year with enough cases of pharmaceutical opioid death in Summit County for analysis, the pharmaceutical opioid overdose death rate in Summit County was 1.53 times higher than the nation as a whole (based on 22 pharmaceutical opioid deaths in Summit County). By 2016, the pharmaceutical opioid overdose death rate in Summit County was 2.86 times higher than the nation as a whole (based on 219 pharmaceutical opioid deaths in Summit County). Further, Summit County has released supplemental reports from the medical examiner's office that provide more detail on overdose death rates using retrospective analysis of the county medical examiner database.[76] This analysis found a total of 1,065 drug overdose deaths in Summit County from January 2009 through December 2016, with a 277% increase in drug overdose deaths by year over the study period. Beginning in 2016, overdose deaths due to high potency opioids (specifically focusing on carfentanil, which is 10,000 times more potent than morphine and 100 more potent than fentanyl) caused 140 deaths, with 47% of those deaths due to carfentanil alone, and 53% positive for other drugs, including but not limited to other opioid drugs. Preliminary data from 2018 indicate some declines in opioid deaths from the 2016/2017 levels,[77] although similar to Cuyahoga county, rates remains much higher overall than a decade ago, indicative of continuing harm.

B.5.2. Because of limitations and gaps in existing surveillance sources, rates of harms based on those sources are underestimates. Important in interpreting the death rates attributed in the vital statistics system to prescription opioids are a number of limitations. Designation of opioid-related harm due to overdose is complicated by the heterogeneous ways in which death certificates are completed across jurisdictions. The designation of an opioid-related death is often determined by "T-codes" found in the ICD-10, to identify the drug(s) involved; however, these codes are inconsistently applied. The publication by Slavova et al. (2015)[3] details the methodological issues with respect to counting overdose cases using death certificates and T-codes. For example, death certificates may be filled out by a coroner or medical examiner, may or may not involve an autopsy and drug testing, and T-codes are inconsistently applied (e.g. if the person filling out the death

certificate does not specify the type of opioid involved in the death, it is often recorded as "other and unspecified narcotic", thus leading to a likely undercount of the number of cases involving prescription or analgesic opioids). Reasonably reliable methods have been developed to estimate corrections for misclassification and missing data.[4] Specifically, Ruhm (2018)[4] used a statistical model to impute data on the involvement of opioid in an overdose death when no drug category is identified on the death record, based on correlates of opioid involvement when the drug class is known. These corrected estimates were used to demonstrate that economic factors explained a small proportion of variance in drug mortality rates, as cited in section B.8. of this report. Thus, while vital statistics estimates may underestimate specific causes of death related to prescription opioids, they provide a reliable source of information regarding opioid-related harms.

B.6. Increases in neonatal abstinence syndrome are another key indicator of opioid-related harm in the population

Neo-natal abstinence syndrome (NAS) occurs when infants are born exposed to opioids in utero and experience withdrawal symptoms after birth. Withdrawal symptoms develop in an estimated 55-95% of opioid-exposed infants, depending on the extent of exposure as well as a range of clinical and demographic predictors, and 30-65% of infants require pharmacological treatment for withdrawal symptoms.[78] NAS is associated with significant medical morbidity, from low birthweight and general discomfort and pain for the infant to medically serious issues such as respiratory disorders and seizures. Cases of NAS can have long-lasting effects on infants, as the clinical literature has documented increased incidence of developmental delays and child behavior problems into childhood.[79] Several large-scale databases have been used to assess trends in NAS, including the Kids' Inpatient Database (KID) and the Nationwide Inpatient Sample (NIS), part of the HCUP family of databases. Available estimates indicate that the rate of NAS per 1,000 hospital births increased from 1.2 in 2000 to 3.39 per 1,000 live births in 2009.[80] An updated publication from the NIS data indicated an increase in NAS from 1.2 per 1,000 in 2004 to 7.5 per 1,000 in 2013 among rural infants, and 1.4 in 2004 to 4.8 per 1,000 in 2013 among urban infants.[81] Further, these data also provided estimates of deliveries complicated by maternal opioid use among delivering mothers, indicating an increase from approximately from 1.3 per 1,000 deliveries in 2004 to 8.1 per 1,000 deliveries in 2013 among rural mothers, and approximately 1.6 per 1,000 in 2004 to 4.8 in 2013 among urban mothers. These estimates are consistent across other data sources. Data from the State Inpatient Databases, also housed in HCUP, documented a 300% increase in the incidence of NAS from 1999 through 2013, from an incidence rate of 1.5 per 1,000 hospital births to 6.0 per 1,000 hospital births in 2013.[82] Thus, these data together show that NAS is dramatically increasing in the United States, because of increases in maternal opioid use at the time of delivery. Children with NAS will require long-lasting monitoring and increased supports through development, long after treatment for NAS and release from hospital care.

B.6.1. Neonatal abstinence in bellwether counties (Cuyahoga and Summit counties) has increased greatly since 2004; rates exceed estimated national averages in Summit County and are consistent with national average increases in Cuyahoga County

Data from the Ohio Department of Health documents discharge rates of NAS in each county. Available estimates indicate that in Summit County, NAS per 1,000 births increased from 2.9 per 1,000 in 2004-2008 to 13.6 per 1,000 in 2011-2015. These are more than twice the national average over the same time period, indicating a high burden of harm even relative to the increasing rates nation-wide. From 2013-2017, 426 infants were diagnosed with NAS in Summit County. In Cuyahoga County, NAS per 1,000 births increased from 1.9 per 1,000 in 2004-2008 to 6.1 per 1,000 in 2011-2015. These rates are consistent with the national average increases, and are indicative of the growing burden of harm nationally. From 2013-2017, 629 infants were diagnosed with NAS in Cuyahoga County.

B.7. Prescription opioid use is causally related to heroin use

The available evidence demonstrates that prescription opioid use causally increases the risk for heroin use. Heroin and prescription opioids have similar pharmacological properties, thus there is the potential for substitution with one or the other when one is unavailable.

The number of individuals who use heroin has been increasing in the United States.[83] Estimates of the number of individuals who use heroin in the US were approximately 100,000 in the 1960s and 1970s, and heroin use was considered largely a problem of urban, low-income areas.[84] However, that has fundamentally changed in the US; as of 2010, available estimates were that there were 1.5 million individuals in the US using heroin at least 4 times per month or more,[85] and there have been increases thereafter in heroin use as well. The demographics of heroin use are also changing, with increases in use across race, social class, gender, and urbanicity.[83,86] The increases in heroin use largely occurred among individuals who use prescription opioid users. Among individuals who use prescription opioids, heroin use increased by 138% from 2002-2004 to 2011-2013, and the connection is particularly strong among young adults.[87] Cross-sectional studies of samples recruited based on non-medical prescription opioid use and/or heroin use consistently find strong signals of a relationship. I reviewed 16 studies that found that individuals who use prescription opioids non-medically have higher rates of injecting and snorting heroin than individuals who do not use prescription opioids, even after controlling for health and mental health, as well as demographics.[86,88–102] While these studies are observational rather than experimental, in that no randomized clinical trial or experimental evidence has examined risk of heroin use following prescription opioid use, the studies are sufficiently diverse in population and design while consistent in their results in order to draw the conclusion that prescription opioid use is causally related to heroin use.

The available data consistently show that approximately 70-80% of individuals who use heroin in the last 20 years started their opioid use with prescription opioids. The most extensive report is from Cicero et al. (2014), reporting on data collected from 2,797 individuals seeking treatment for opioid use disorders.[86] Cicero et al. (2014) demonstrated that among those who initiated opioids in the 1960s through 1980s, less than one third used prescription opioids before heroin. From the 1990s on, as the supply of opioids increased, so too did the proportion of individuals who use heroin who began opioid use with prescription opioids (among those initiating in the 1990s, 50%; 2000s, 85%; 2010s, 78%). The figure that approximately 70-80% of individuals who use heroin begin with prescription opioids has been replicated in numerous other studies. Lankenau et al. (2012)[89] examined drug use histories among 50 individuals who inject drugs who had non-medically used opioids in the three months prior to the study, and documented that 86% of the sample used opioids non-medically prior to heroin use. Further, while individuals who use non-medically obtained opioids from a variety of sources including dealers, family, and friends, 75% of these individuals who use non-medically had obtained a prescription for opioids during their lifetime. Pollini et al. (2011)[93] studied 123 individuals who inject heroin, documenting that 39.8% reported prescription opioid use prior to heroin use. Mateu-Gelabert et al. (2015)[94] interviewed 46 individuals who inject heroin, 70% of whom initiated opioid use with prescription opioids; mean age of first prescription opioid use was 17.9, and heroin use was 18.8 years; among individuals who use prescription opioids and heroin, the average difference in mean age of initiation between prescription opioids and heroin was 1.3 years. Ethnographers in Philadelphia, San Francisco, Wilmington, and, importantly for the present case, Ohio, documented trajectories from medical and non-medical prescription opioid use to heroin, especially among younger cohort members.[90,95,96] Specific to Ohio, an early case report from the Ohio Substance Abuse Monitoring Network published in 2003 interviewed 10 individuals who use heroin and found that five of the 10 reported OxyContin use before heroin use.[96]

While studies of individuals who use heroin and other opioid interviewed about their drug use histories provide another signal, still more evidence from large-scale surveys and cohort studies has documented the relative risk of initiating heroin given prescription opioid use, compared to individuals who do not use prescription opioids. I cited above the evidence among adolescents and young adults that has found strikingly high estimated incidence rate ratios for the transition to heroin given non-medical prescription opioid use, even when controlling for individual-level risk factors that underlie a proclivity for drug use overall. There are also numerous studies that demonstrate strong relationships between non-medical prescription opioid use and heroin use among adults. Muhuri et al.[97] documented the association between prescription opioid use and heroin initiation estimated from age of onset reports across 9 years of the National Household Surveys on Drug Use and Health. Pooled analyses indicated that the risk of heroin initiation was 19 times higher among those with prior non-medical prescription opioid use compared to those who did not use, even after

controlling for a range of factors involved in the drug taking behavior. Banerjee et al. 2016[98] found that non-medical prescription opioid use was associated with more than 5 times increased hazard of heroin initiation compared to no use, even after adjusting for multiple risk factors. Of those who reported new onset non-medical prescription opioid use, 27% subsequently initiated heroin.

Several additional points are worth keeping in mind. A small proportion of individuals who use prescription opioids progress to heroin use.[97] However, the number of individuals who use prescription opioids is approximately seven times larger than the number of individuals who use heroin, thus while the absolute risk of transitioning to heroin given prescription opioid use is relatively small, the vast majority of individuals who use heroin began with prescription opioid use, and even small increases in progression to heroin use creates a significant public health burden.[87] Reasons cited for the transition to heroin use given prescription opioid use based on the research cited above is most often cost and convenience reasons; prescription opioids are more expensive to obtain illegally than heroin, and more difficult in many geographic areas. Numerous factors predict transition from prescription opioid use to heroin use, including individual-level and community-level characteristics. However, the proportion initiating heroin increases in a dose-response relationship with the extent and length of prescription opioid use, providing further support for a causal relationship. Based on the evidence, it is reasonable to conclude that there is a causal relationship between prescription opioid and heroin use, and that the increases in population-level heroin use in the United States are due, at least in part, to individuals who use prescription opioids transitioning to heroin use.

Finally, since approximately 2013, overdose deaths due to synthetic opioids (e.g. fentanyl) have been exponentially increasing in the United States. These synthetic opioids are much more potent than heroin; less than 2 mg of fentanyl, equivalent to approximately two grains of salt, can cause overdose.[103] Available evidence indicates that fentanyl and other highly-potetent opioids have been adulterating the supply of both heroin and illicitly manufactured prescription opioids.[104] Given the evidence that prescription opioid use is causally related to heroin use, prescription opioid use is also responsible for the increase in fentanyl and other synthetic opioid harms. Indeed, individuals who use prescription opioids who both obtain illicitly manufactured prescription opioids as well as heroin will be potentially exposed to fentanyl, increasing the risk of overdose and death. In terms of the magnitude and scope of the relationship, given that available estimates indicate that approximately 80% of individuals who use heroin begin their opioid-using trajectories with prescription opioids, I estimate that approximately 80% of fentanyl-involved deaths are attributable to prescription opioid use.

B.8. The uptake of diverted opioids was not random, but part of a complex system that involved community level economic conditions

The exponential increases in the opioid supply, and the resulting opioid diversion and related harms, did not occur in isolation. It is important to put in context that opioid use disorder and overdose disproportionately affected economically deprived areas, and also interacted with individual-level risk factors for use. However, ready access to prescription opioids was a necessary precondition to their widespread availability and uptake.

The relationship between shifting macroeconomic conditions and drug poisonings has received considerable attention since the publication of Case and Deaton's widely-discussed paper.[105] In their 2015 paper, Case and Deaton reported a recent spike in mortality rates among less-educated non-Hispanic Whites, and posited that long-term shifts in the labor market, reduced employment opportunities, and overall life prospects for persons with a high school degree or less, have driven increases in "deaths of despair" (i.e., deaths from suicides, cirrhosis of the liver, and drug poisonings). This model suggests that the increased rates of opioid-related mortality over the past three decades are attributed to shifting macroeconomic conditions. However, several studies contradict the narrative that the rise of deaths in the US is due to a common source such as "despair". In a working paper by Ruhm (2018),[4] known measures of economic factors predicted drug and opioid overdose, but explained very little of the variation in rates over time. Further, Masters et al. (2018)[106] reanalyzed vital statistics data by gender, age, and birth cohort, and concluded that drug overdose rates increased across a wide range of age groups, especially those in young and middle adulthood, and did not

mirror trends for other "despair"-related death such as suicide, indicating that the drivers of opioid-related deaths in the US were factors that could influence a broad range of age groups simultaneously.
I have reviewed four published studies,[4,107–109] to date, which have examined the effect of macroeconomic conditions on drug-related mortality rates. One of these studies[107] found that average drug-related mortality rates were higher in counties with greater economic and family distress and in counties with greater population share dependent on mining, compared to other areas of the labor market, and lower in counties with more religious establishments, higher percentage of recent in-migrants, and counties with greater population share dependent on public sector employment; two other studies[105,108] found that a 1% increase in county unemployment rate was associated with a 0.19 per 100,000 increase in opioid-related mortality rate (3.6%) and that the estimated change in mortality accounted for by worsening economic conditions ranged from 5 to 7% for Prescription Opioid-related mortality and 2 to 5% for illicit opioid-related deaths at the 3-digit ZIP code level, indicating that economic conditions account for less than one-tenth of the rise in mortality rates over time. Finally, Pear et al.[109] found that two area-level indicators, percent in poverty and percent of adults with less than a high school education, were associated with higher rates of prescription opioid related mortality, while median household income was associated with lower rates. However, urbanicity modified the association between macroeconomic conditions and rates of heroin-related mortality, with poverty and unemployment associated with increases in heroin-related mortality in metropolitan areas and low educational attainment alone associated with heroin-related mortality in rural areas. Limitations of the extant research are that publicly released files do not include all deaths (to reduce the potential for confidentiality violations),[107] inadequate measure of outcome,[107] failure to account for area-level prescription opioid supply,[107,109] and no investigation of the stability of effect estimates at different levels of organization.[4,107–109]

In summary, there is evidence that the population distributions of prescription opioid and other opioid mortality disproportionately affected economically deprived areas; however, the available evidence indicates that economic conditions played a relatively small part in increased opioid-related morbidity and mortality. The driving force in increasing opioid-related morbidity and mortality was access to and wide-spread availability of opioids.

B.9. Availability theory and the relationship with harms related to prescription opioids

Arguments have been made that the increases in prescription opioid overdose and addiction in the US are largely driven by non individuals who use non-medically, and that as prescription opioids have become more difficult to obtain because of changes to the changes to prescription opioid supply (e.g., prescription drug monitoring programs, physician education), those who use drugs have progressed to heroin and other more available and less expensive opioids to satiate addiction. While certainly there is data that rates of overdose, addiction, and harm among those who use non-medically are opioids are high, there is evidence that harm among those who use medically is also high. Further, as the data cited in this report show, the proportion of individuals with opioid use disorder that receives a prescription at some point from a physician is more than half, and the risk of addiction given medical use of opioids at high doses for long periods of time is also between 10 and 20 times that of low dose prescriptions. Rates of opioid distribution and opioid related death vary substantially across geographic areas, and all available evidence indicates that prescription opioids harms, due to medical use as well as diversion, increase with the supply of opioids. With regard to recent decreases in the opioid supply, there is evidence that restricting the prescription opioid supply is associated with greater transition to heroin,[110] and that this transition has influenced death rates due to the contamination of heroin with fentanyl and other synthetic opioids. As such, abatement that is broad ranging in scope is necessary. However, the notion that the current opioid epidemic is due to economic conditions or despair/depression is not supported by data. There is no evidence that depression has increased across time among adults in the US, and available evidence from economic studies of the role of economy in drug overdose have suggested that there is a limited role for economic conditions; based on the studies and data discussed above, the role of opioid supply is so much more strongly correlated that no reasonable interpretation of the data would support the conclusion that economic conditions are greater than supply in producing the observed trends.

Indeed, there are decades of public health research that have a strong analogy to the current opioid epidemic. The relationship between supply of an addictive substance and subsequent rates of substance use disorder has been well established in the public health literature for years, under the model of "availability theory".[111] Succinctly, this theory posits that one driver of population burden related to substance use harm is the availability and cost of the substance.[112,113] The relationship between availability/cost and harm has been extensively documented for decades for alcohol and tobacco, and is one reason that alcohol and cigarette taxes, minimum pricing, and other public health efforts aimed at availability and price are among the most effective population level interventions to reduce alcohol-related harms such as alcohol-impaired driving fatalities.[114–116] Put in that lens, as prescription opioids became more commonly available in the market, availability theory would predict a rise in opioid-related harm.

B.10. Comparison of deaths due to prescription opioids with NSAIDs

Among the threads of inquiry related to the increases in opioid-related harm in the United States are comparisons to harm associated with other pharmaceutical products that also cause harm in some users. For comparison, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for a range of conditions, including pain, but also arthritis and other inflammatory conditions as well as fever. Common forms of NSAIDs are available over-the-counter, such as aspirin and ibuprofen, but a range of products are available by prescription as well. NSAIDs are prevalent, and their use varies across age. Data from the National Health and Nutrition Examination Surveys from 1999-2004 indicated a past-year prevalence of 26.1% of the US population for all NSAID use, and 9.5% for prescription NSAID use.[117] While use is common, it comes with health risks, including, for example, cardiovascular events. Available reviews and meta-analysis suggests that the risk of serious GI events with extended NSAID treatment is between 1-3%, which is approximately 10 times higher than the background rate in the population.[118–122]

Given their potential for harm and that both are used to treat pain, it is worth comparing the deaths due to NSAIDs with the deaths due to prescription opioids. It has been estimated that 16,500 per year are due to GI bleeding from NSAID use. This estimate, however is not reliable. It is based on a single article that extrapolated from 19 deaths among 4,258 patients in an administrative database,[123] multiplying the 19 deaths by estimated population size. Such extrapolation is not quantitatively specific due to measurement error in death rates, and further, the cohort from which the 19 deaths were observed was among a sample with rheumatoid arthritis, among whom the baseline mortality rates are higher than the general population. Another study estimated deaths due to NSAIDs to be closer to 3,200 deaths,[124] but this too is not a reliable estimate. The estimate of 3,200 deaths is based on the estimate of the attributable fraction for NSAID and death. The attributable fraction (an estimate of the proportion of deaths that are causally related to an exposure) varies based on the baseline prevalence of exposure. Thus, authors multiplied the attributable fraction in the study sample by the proportion of the US population that used any NSAID in the previous week (regardless of dose or duration), based on a phone survey of 2,590 individuals, which is not a large sample size for total population extrapolation. Further, applying a summary attributable fraction is incomplete, as it does not take into consideration type and dose (e.g. any NSAID use counts at the same level of risk as long-term use); b) it is well known that the prevalence of NSAID use varies widely by race, sex, and age,[117] such that applying one average to the whole population without incorporating subgroup heterogeneity will include substantial error.

Solomon et al. (2010)[125] directly compared the risks associated with NSAID to those with prescription opioids as well as cyclooxygenase 2 inhibitors (coxibs) among a large claims database of low-income older adults who were Medicare beneficiaries in Pennsylvania and New Jersey and had diagnoses of osteoarthritis or rheumatoid arthritis on 2 separate visits (N=36,414). Authors used a propensity score to balance potential confounding factors among those using NSAIDs, coxibs, and opioids. The use of a propensity score in this analysis is important and rigorous, as it controls for the potential reasons why an individual would be prescribed, for example, NSAIDs over opioids. Once matched on propensity scores, the three groups were balanced on over 40 covariates including demographics, clinical characteristics, health history, and use of

other medications. Further, authors included incident use of medications in the comparison groups, which further helps to establish causality, and examined incident health events. Comparing prescribed NSAIDS to prescribed opioids, those prescribed opioids had higher rates of a range of adverse events including cardiovascular events, fractures, kidney injury and falls, and approximately equivalent rates of events such as GI bleeding. And finally, the mortality rate among opioid users was 75 per 1000 patient years among prescribed opioid users, compared to 47 per 1000 patient years among prescription NSAID users over the course of the study, for an increased hazard of death of 1.87 times that of NSAID users. While the particular hazard ratios may differ in other populations, there is no *a priori* reason to doubt the applicability of Solomon *et al's* general conclusion that prescription opioids are associated with greater incidence of adverse events and mortality. With that in mind, however, Solomon et al. (2010) remains the most rigorous study to date that has directly compared the harm of medical prescription opioid use with medical NSAID use, and determined that mortality as well as a wide range of medical morbidities was higher, substantially so, for opioids compared with NSAIDs.

C. Interventions to ameliorate the opioid epidemic

Lessons learned from the successes and failures of previous epidemics have demonstrated that the existence of an effective biomedical treatment, as well as harm reduction strategies, are part of the strategies that are necessary to ameliorate the epidemic. These strategies work alongside other interventions to reduce supply, reduce demand, and enforce control and prevention strategies that reduce criminal activity, across a wide range of other systems approaches. Yet, within the systems that need to be engaged in ameliorating the epidemic, biomedical treatment and harm reduction are among those that have demonstrated success. In this section, I detail the evidence for medication assisted treatment (MAT), as well as harm reduction resources of naloxone access and needle exchange, including an assessment of the level of need in Cuyahoga and Summit counties.

It is important to note that interventions to reduce the supply and control prescriptions of opioids are already in effect in Ohio, including a prescription drug monitoring program, as well as efforts to improve provider education, prescribing guidelines, and drug disposal facilities for unused opioids. However, the needs of these counties surpass these programs. Data from the Cuyahoga County Medical Examiner's Office, for example, indicates that 52% of overdose decdents had no record in the prescription drug monitoring program in 2016, and 29% had no record in 2017, suggesting that monitoring programs alone are insufficient for abatement.[74] These programs and policies will not be reviewed in this report; rather I will focus on the evidence for a three-point abatement plan: medication assisted treatment (MAT), harm reduction through naloxone availability, and synthetic opioid testing and warning systems as part of an abatement strategy. Other programs and policies have also been implemented, and my focus on these aspects is intended to be illustrative rather than exhaustive.

C.1. Medication Assisted Treatment (MAT) is effective in reducing opioid use disorder and overdose

Medication Assisted Treatment (MAT) is a critical component of treatment scale-up needs for the existing population of individuals with opioid use disorders.[126] Numerous medications with high quality evidence base for treatment of opioid use disorder include opioid agonists, partial agonists, and antagonists, and can be used in combination and at various points along the treatment cascade effectively. Three medications in particular have been the focus of MAT programs: methadone, buprenorphine, and naloxone.

Methadone is among the most commonly used medications to assist with recovery from opioid use disorder. Approved by the Federal Drug Administration in 1972, methadone is an opioid agonist which prevents withdrawal symptoms and intense craving when discontinuing other opioid use without concomitant experiences of euphoria. Methadone maintenance is a sequence of physician-monitored methadone prescription that provides sufficient doses of methadone, provided to the patient in timed intervals, and adjusted per withdrawal and other symptoms. To date, eleven randomized controlled trials of methadone maintenance compared with standards of care (either placebo or non-pharmacological therapy) have met

standards of high levels of evidence.[127] A recent meta-analysis of these eleven trials, including data on 1,969 unique patients, concluded that there is strong evidence that methadone maintenance therapy is safe and effective for treatment of opioid use disorder. Indeed, meta-analytic estimates suggest that relapse to opioids was 0.66 times lower in groups randomized to methadone maintenance compared with other standards of care; estimates for occurrences of criminal activity and mortality were lower in methadone maintenance groups as well, although the low number of overall events in both groups made statistical quantification of the risks across groups less reliable. Overall, however, there is strong evidence for the efficacy of methadone to treatment opioid use disorder.

More recently, buprenorphine, a partial opioid agonist, was approved for use as an opioid use disorder therapy in 2002. Buprenorphine differs from methadone in the binding and activity in the mu-opioid receptor, but reduces withdrawal symptoms and craving during cessation of other opioid use. Buprenorphine has a lower addiction and overdose risk than methadone due to the ceiling effect of the partial agonist, insofar as taking more opioids will not enhance the effects of buprenorphine. MAT protocols for buprenorphine allow for office-based outpatient care and dispensing, and buprenorphine is available in a number of delivery systems, including sublingual tablets, buccal patches, and implants. Like methadone, there is a high level of evidence for the effectiveness of buprenorphine in recovery from opioid use disorder. Twenty-four randomized controlled trials have compared outcome of patients randomized to buprenorphine maintenance versus placebo or methadone maintenance.[128] Meta-analysis of these trials indicates that buprenorphine is more effective than placebo in retaining patients in treatment and reducing opioid relapse, especially at high doses. When compared with methadone maintenance, buprenorphine is as effective or slightly less effective, depending on the level of opioid use disorder and the dose patterns of opioids among patients entering treatment. Moreno et al. reported in a retrospective chart review of 470 adults admitted to a hospital that buprenorphine use was associated with reductions of by 53% and 43% in 60 and 90 day readmission rates, respectively.[129] Further, both methadone and buprenorphine treatment are associated with long-term (>4 years) retention in treatment, and reduced relapse.[130]

Finally, naltrexone differs from both methadone and buprenorphine in that it is an opioid antagonist; it produces no opioid-like effects, has no abuse or addiction potential, and blocks the exogenous effects of other opioids. Naltrexone cannot be initiated until patients are fully detoxified from opioids without rapidly precipitating withdrawal symptoms. Naltrexone is available in a various of modes of administration, including oral tablets as well as long-term naltrexone implants, and in a monthly extended-release form. Clinical trials with high levels of evidence support the use of naltrexone for the treatment of opioid use disorders, with sufficient evidence concluding lower rates of relapse compared to placebo.[131–136] However, naltrexone is associated with higher rates of overdose after cessation of treatment,[137] further, naltrexone is more difficult to successfully initiate given the need for complete detoxification prior to initiation; once initiated, however, available evidence indicates similar performance of MAT therapies in terms of retention in care and reduced relapse, especially for extended-release naltrexone.[138]I

In summary, MAT is safe and effective compared to no treatment, and a wide variety of protocols are available, depending on patient characteristics and presenting symptoms. Patients on MAT report greater quality of life when in treatment,[139] and the efficacy in reducing mortality rates at the population level stand as a testament to the need for increased access to MAT.[140] As the name implies, "Medication-*Assisted*-Treatment" means that the medications are used along with other treatment methods, rather than in isolation. For example, a recent authoritative review of MAT studies stated, "MAT is a stabilizing addition to relapse-prevention counseling and mutual help groups (such as Narcotics Anonymous) in that it increases the effectiveness of those interventions."[141]

C.2. Increasing MAT access is critical to amelioration of opioid-related harms

Expanded access to MAT is associated with reduced mortality rates at a population level,[140] as well as reduced hospital readmission rates. Delivery models of MAT are well developed and heterogeneous, depending on the

patient population and structural issues in access to various medication types.[126] Among the most promising delivery modalities is the hub-and-spoke model, which features a "hub" of care that offers intensive support as well as a range of MAT, with a much more substantial number of "spokes" that can be disseminated to more rural and less populated areas that would provide routine medication therapy and less intensive care. In Vermont, the hub-and-spoke approach was associated with reductions in relapse, greater retention in care, and significant reductions in overdose, emergency department utilization, arrest, and family conflict.[142] Similar hub-and-spoke systems are under consideration in other jurisdictions. Indeed, perhaps the most compelling issue in identifying and treating individuals with opioid use disorders is not whether there are medication regimens with well-evidenced effectiveness, but that the resources to treat all of those in need are simply not available. Approximately 80% of individuals with opioid use disorders are estimated to receive no treatment, and the proportion lacking access varies across geographic areas. Among adolescents, a population whose years of life lost due to opioid overdose is greatest, access to MAT is even more rare; available estimates indicate that even among adolescents in treatment for opioid use disorders, 2.4% of those with heroin addiction received MAT, and just 0.4% of those with prescription opioid addiction received MAT.[143] Access to treatment is not randomly assigned, and barriers to access cross multiple levels or organization, cultural, social, economic, and structural barriers to access to care. In areas where MAT is available, studies already reveal age-based, racial, and ethnic disparities in treatment engagement and completion. There remains a major gap in trained providers,[144] as well as stigma associated with the treatment and prognosis of individuals with opioid use disorders.

Available estimates by state indicate that MAT needs far outpace the number of available providers and the number and diversity of needed programs in order to treat all those affected.[145] While trends indicate promise with expansion of services in many states, major gaps remain. Most states have expanded coverage of and access to opioid agonists from 2004 through 2013, although states still vary widely in barriers to accessing the available coverage.[146,147] Studies of specific geographic areas have demonstrated increases in access to and uptake of buprenorphine; for example, in a large urban area, between 2004 and 2013, buprenorphine compared to methadone treatment increased over time; however disparities remained, as buprenorphine access increased the most in the most advantaged neighborhoods.[148] Nevertheless, increased access to MAT is associated with greater rates of individuals with opioid use disorders entering and being retained in treatment.

C.3. MAT coverage and needs in Cuyahoga and Summit counties

Given that barriers to MAT are predominantly access to providers, it is important to assess the needs of Cuyahoga and Summit counties in terms of the density and location of MAT providers to fill the need for all of those with opioid use disorders in the community. Data on the current number of individuals receiving MAT treatment can be drawn from a number of sources; in Ohio as a whole, data from Medicaid beneficiaries indicated that among beneficiaries with an opioid-related diagnosis, approximately 50% received at least some MAT in 2016,[149] equivalent to approximately 48,000 individuals (which, conversely, indicates that approximately half of individuals with an opioid-related diagnosis Medicaid beneficiaries are not receiving MAT).

While the number of individuals currently living with opioid use disorder in Cuyahoga and Summit counties is unknown, I can provide an estimate of the number given the number of overdose deaths. Individuals who potentially need MAT include both those with diagnosed opioid use disorders, as well as those estimated to be regular users of opioids. I include the estimated regular users of opioids in this estimate for two reasons. First, addiction rates among regular users of opioids is high, as reviewed in Section B.2. Second, while protocols for tapering dose among regular users of opioids who may be physically dependent on opioids but without opioid use disorder are appropriate,[150] MAT may be indicated depending on the level of the dose. Thus, MAT should be available in the circumstance that tapering is not effective or indicated in reducing dose. Degenhardt et al. (2011)[151] published a systematic review and meta-analysis of the overdose mortality rate of individuals who were dependent or regular users of opioids. Based on analysis of 39 cohort studies,

Degenhardt et al. (2011) estimated an overall drug overdose death rate (including opioids as well as other drugs) of 0.65 per 100 person-years of observation, with a confidence interval between 0.55 and 0.75 overdose deaths per 100 person-years. That is, if 1000 people who were dependent or regular users of opioids were observed for one year, I would expect between approximately 5 and 8 overdose deaths. While Degenhardt et al. (2011) reported all drug overdose, the majority of those overdose deaths can be estimated to be due to opioids. In the United Sates, for example, 63% of overdose deaths as of 2015 involved opioids (note, this estimate includes all deaths in which there was a code for opioid use on the death certificate, regardless of other drug use),[62,152] indicative of the high contribution of opioids to overdose death and the rationale that each drug contributed to the death in a multi-drug death). The proportion of overdose deaths involving opioids among regular or dependent individuals who use opioids is likely even higher, given the opioid overdose risk.[153] The proportion of deaths due to opioids is not relevant for my estimation process, however, given that I am estimating the pool of regular or dependent individuals who use opioids from the total for all overdose death. Nevertheless, we note that, while not included in the estimation, the majority of those overdose deaths are estimated to be due to opioids. Note, that the Degenhardt et al. study was published before the outbreak of fentanyl-induced deaths, so the estimated overdose death rate of 0.65 per 100,000 it is likely an underestimate of the total mortality risk among current opioid users. Further, Degenhardt et al. examined the risk for all overdose deaths regardless of the drug that caused the overdose (though again we note that the majority of the overdose deaths, especially among regular or dependent users of opioids, is estimated to be the majority of cases);[152] thus, the rate of 0.65 per 100,000 would include overdose deaths from opioids as well as other drugs. To summarize, 0.65 per 100,000 is the overall overdose death rate *among regular or dependent users of opioids*; thus, dividing the number of total overdose deaths (including but not limited to opioids) by 0.65 per 100,000, I can obtain an estimate of the estimate size of the population of regular or dependent users of opioids.

I estimated the population size of individuals who are dependent or regular users of opioids in Cuyahoga and Summit counties by applying the estimated death rate of 0.65 per 100 person years to the number of overdose deaths, dividing the number of overdose deaths by the rate of expected overdose to estimate the size of the user pool. Because fentanyl increases overdose death, I used 2013 estimates of the number of overdose deaths to more closely approximate the anticipated death rate prior to fentanyl deaths. Applying this methodology to the United States as a whole, in 2013 there were 43,982 drug overdose deaths in the United States,[154] which at a rate of 0.65 per 100,000 deaths among dependent or regular users of opioids would estimated 6,766,461 individuals in the US who have opioid use disorders and/or are regular users of opioids. Comparing that figure to the National Household Survey on Drug Use and Health, for 2015,[155] NSDUH data estimated that approximately 11 million individuals reported past-year prescription opioid misuse, 2.0 million met criteria for prescription opioid use disorder, and 0.3 million were heroin users. Given that the range from prescription opioid misuse to prescription opioid use disorder was 2.0 to 11 million, my estimate of approximately 6.7 million regular and/or dependent users of opioids is within the range of other national data. Further, given that the NSDUH survey sampling frame is individuals residing in households and group quarters, the survey likely underestimate the total population of individuals who are regular/dependent users of opioids in the United States, underscoring the importance of the method that I use here.

Further, a study based on medical records of 9,940 insured individuals who received 3+ opioid prescriptions within 90 for noncancer pain found that the rate non-fatal to fatal overdoses was approximately 7 non-fatal overdose for each fatal overdose.[156] I used this as a conservative estimate of the potential burden of non-fatal overdose in the counties; the estimate is conservative given that non-fatal and fatal overdoses have increased exponentially since 2013 given the contribution of synthetic opioids such as fentanyl to overdose morbidity and mortality. Thus, the total burden of non-fatal overdoses will likely be greater than estimated here.

Cuyahoga County. In Cuyahoga County in 2013, there were 340 overdose deaths.[157] Based on an anticipated death rate of 0.65 per 100 person years, I would estimate that the total size of dependent or regular users of opioids is 52,307. Applying the confidence intervals of 0.55 to 0.75 per 100 person years, I would estimate that the total size of dependent or regular users of opioids is between 45,333 and 52,307, and that this is the

number of individuals who are in need of MAT access in Cuyahoga County. Further, given the estimated 7 to 1 ratio of non-fatal to fatal overdoses, I would estimate that there can be an expected minimum of 2,380 non-fatal overdose events per year. However, these estimates should be considered conservative; they are based on data collected before the adulteration of the heroin and illicit prescription opioid supply with high potency synthetic opioids.

Summit County. In Summit County in 2013, there were 75 overdose deaths based on vital statistics, which is corroborated by supplemental analyses of overdose deaths published by the Summit County Medical Examiner's office.[76] Based on an anticipated death rate of 0.65 per 100 person years, I would estimate that the total size of dependent or regular users of opioids is 11,538. Applying the confidence intervals of 0.55 to 0.75 per 100 person years, I would estimate that the total size of dependent or regular users of opioids is between 10,000 to 13,363, and that this is the number of individuals who are in need of MAT access in Summit county. Further, given the estimated 7 to 1 ratio of non-fatal to fatal overdoses, I would estimate that there can be an expected minimum of 525 non-fatal overdose events per year. However, these estimates should be considered conservative; they are based on data collected before the adulteration of the heroin and illicit prescription opioid supply with high potency synthetic opioids. Available data in Summit County indicates that MAT utilization is not currently adequate for abatement and treatment of those in need; available data indicate that there were 2,072 individuals receiving MAT in Summit County.[158]

C.4. MAT effectiveness and opportunities among high-priority populations

In addition to the need for MAT access among all those with opioid use disorder, extensions of access to MAT treatment are particularly important for three high-priority populations: jail/prison populations, those in the child welfare system, and pregnant women.

C.4.1. Jail/prison populations

Individuals in jails and prisons are more likely have opioid use disorders than individuals in the general population, by a factor of at least 15 to 1,[58,59] and the criminal justice system is an opportunity to address and reduce opioid use disorders during incarceration. The period of incarceration is a critical one for opioid-related harm; forced or abrupt cessation of opioids upon incarceration may elicit serious and medically dangerous withdrawal symptoms, and access to opioids within the system to manage withdrawal or for euphoria may be even more dangerous. Prisoners are at higher risk for overdose in the immediate time after release, due to tolerance decreases during incarceration and high risk of relapse after release. A meta-analysis of six studies found that in the two weeks after release from prison, the overdose rate among the formally incarcerated is 3-8 times higher than the following ten weeks after release.[159] Yet, despite a much greater burden of harm, an estimated 75% of inmates in the US do not receive treatment for drug use disorders during or after release.[58] Available evidence within criminal justice populations indicates that MAT is effective within these systems. For example, over a 24-week study period, a clinical trial randomizing 300 individuals to extended-release naltrexone versus no medication found that there were no overdose events among those on naltrexone, compared to 7 among those with no medication.[132] Further, available evidence indicates that among prisoners given methadone during incarceration, post-release mortality was approximately six times lower when MAT continuation was provided compared to abrupt cessation, and that MAT during incarceration is associated with an 85% reduction in fatal overdose in the month after release.[160–162] Still more studies have found that MAT access among incarcerated persons is associated with continued, reduced relapse, and reduced risk of overdose after release.[134,160,163–168]

Importantly, expanding access to MAT in prison populations has been demonstrated to be effective in reducing opioid-related harms. In 2016, Rhode Island Department of Corrections (RIDOC) initiated a new model of screening and protocoled treatment with MAT (i.e., methadone, buprenorphine, and naltrexone), whereby persons arriving into the system receiving MAT were maintained on their respective medication regimen, without tapering or discontinuation of medication, and persons released into the community were

provided referrals and transition to a system of 12 community-located Centers of Excellence in MAT. Inmates were twice as likely to receive MAT monthly during the post-implementation period (January-June 2017) compared to the pre-implementation period (January-June 2016), 39% compared to 18%, respectively. Second, a 60% reduction (95% CI, 19%-82%) was reported in post incarceration deaths from drug poisonings among inmates released from incarceration after implementation of the comprehensive MAT program. In addition, the study found time since release from incarceration to death was longer in 2017 (n=190 days) than 2016 (n=112 days) and (b) among those who did die, fewer died within the first 30 days of release from incarceration in 2017 (11%) compared to 2016 (38%).[168] Connecticut and Vermont are now developing and implementing versions of the Rhode Island model.

In sum, jail and prison populations have a high burden of opioid use disorders; overdose and other opioid related harms are higher in prison and after release if no MAT services are provided; MAT service provision in jail/prison as well as continuity of care after jail/prison is highly effective in reducing morbidity and mortality, and states that have adopted comprehensive opioid care packages for prisoners have had public health success.

C.4.2. Jail/prison populations and MAT needs in Cuyahoga and Summit counties

I estimated the number of inmates in jail and prison within a given year in Cuyahoga and Summit counties, in order to estimate the burden of need for MAT services in these counties.

Cuyahoga County. In 2015, the average daily population of Cuyahoga County jails was 2,020 individuals.[169] Given that rates of opioid use disorder are an estimated 15-times higher in jail/prison populations than the general population, I can infer that MAT services would be in high demand at Cuyahoga County jails and prisons, as well as continuity of care after release.

Summit County. In 2017, there were approximately 647 individuals in Summit County jails per day.[170] Given that rates of opioid use disorder are an estimated 15-times higher in jail/prison populations than the general population, I can infer that MAT services would be in high demand at Summit County jails and prisons, as well as continuity of care after release, which would include referral and access to MAT providers, at a minimum, as well as referral and access to outpatient treatment services that would include therapy and social work services.

C.4.3 Child welfare system

An estimated 442,995 children were in the foster care system in the US as of 2017, and of the 269,690 who entered the system in 2017, 39.3% of those cases were due to parental substance use disorder.[171] Estimates indicate that approximately 50-80% of families involved in the child welfare system include parents with substance use disorders, regardless of whether the substance use was the primary reason for the removal of the child from the home. Reunifications between parents and children are lower in the context of parental substance use disorders, and reunifications are even lower when the substance involved is opioids. Available evidence indicates that child welfare caseloads are positively correlated with indicates of opioid-related harms, including the rate of drug overdose deaths and non-fatal hospitalization.[172]

MAT access within the child welfare system is associated with lower rates of relapse among parents, and higher rates of family unification, although MAT access remains low among child welfare involved parents. For example, a study of 596 parents with a history of opioid use in the child welfare system found that just 9.2% received MAT, and that additional months of MAT receipt were associated with increased odds of child custody retention.[173] Reviews of the literature on child outcomes among parents engaged with MAT find generally that both parental and child wellbeing outcomes improve with length of time on MAT.[174] Expanding access to MAT within the child welfare system will require investment, given that the expanded number of child welfare cases already overwhelms a generally underfunded and understaffed system, and that

continuity of care and collaboration across child welfare and medical systems can be a challenge, and families often have the burden of multiple morbidities including mental health challenges as well as opioid use disorders. Yet these challenges are being addressed; starting in 2019, federal reimbursement for evidence-based substance use treatment, such as MAT, will be available within state child welfare agencies;[175] however, reimbursement is only possible when there are sufficient providers of MAT to meet the need, and continuity of care and referral of parents and caregivers in need of services, thus increased capacity for referrals to and access to MAT services are needed.

F.4.4. Child welfare system and MAT needs in Cuyahoga and Summit counties

Cuyahoga County. From 2002 to 2017, approximately 20,162 children were engaged in the child welfare system through a variety of mechanisms including transitional housing and inpatient treatment,[171] with 1,333 entering out of home care in 2017 alone. Further, 2,100 children and teens were in temporary or permanent custody outside of the home, the highest levels since 2011.[176] With an estimated 50-80% of those families experiencing substance use disorders among the parents, I would anticipate that approximately 667-1,066 children are in families in the child welfare system per year in need of access to MAT.

Summit County. From 2002 to 2017, approximately 14,663 children entered out of home care, with 672 entering out of home care in 2017 alone.[171] Further, in 2016, the average number of children in foster care in Summit County was 675, and 737 children on average were in temporary or permanent custody outside the home. The average monthly number of children in custody, which means they are taken from their homes, has increased from 601 in 2015 to 737 in February of 2018.[177] While the percentage of these child welfare cases that were opioid involved is not available, 50% of emergency custody cases involved substance abuse and 25% of those involved opioids.[178] With an estimated 50-80% of those families experiencing substance use disorders among the parents, I would anticipate that approximately 336-578 children are in families in the child welfare system per year in need of access to MAT.

F.4.5. Pregnant women with opioid use disorders

Women who become pregnant during opioid use disorders are at increased risk of harm to themselves and their fetus. Opioid use disorders increase the risk of miscarriage and stillbirth; abrupt cessation of opioids is associated with preterm labor and fetal distress. Among those infants who are live born, prenatal exposure to opioids can cause neonatal abstinence syndrome (NAS) among newborns, a painful condition associated with opioid withdrawal symptoms and in some cases causing seizure, respiratory conditions, and other severe outcomes. MAT is approved and recommended for pregnant women to reduce adverse events during and after pregnancy for women and their offspring, and the use of methadone, buprenorphine, and naltrexone during pregnancy is not associated with specific adverse outcomes, though infants exposed to opioid agonists may experience neonatal abstinence syndrome. Three randomized controlled trials and eight prospective cohorts have examined fetal outcomes of comparing specific modalities of MAT,[179] specifically methadone to buprenorphine, and have generally found that both are effective, with some data suggesting that buprenorphine is associated with less NAS and shorter hospital stays. Generally, reviews and meta-analyses find that buprenorphine during pregnancy is better tolerated and associated with fewer adverse outcomes, though many trials have found no significant differences.[180] Given the weight of the evidence in favor of MAT during pregnancy, national regulatory guidelines have been established to guide clinicians and other care providers on the safe and effective introduction and maintenance of pregnant women on MAT.[181] In summary, women with opioid use disorders who engage in MAT during pregnancy have better outcomes for themselves and their children, compared to abrupt discontinuation of opioids or continued non-medical use.

F.4.6. Pregnant women with opioid use disorders and MAT needs in Cuyahoga and Summit counties

Pregnant women in Cuyahoga and Summit county who have opioid use disorders should have early and available access to MAT. In a previous section, I outlined the rates of neonatal abstinence syndrome in Cuyahoga and Summit counties. These estimates provide a lower bound of the medical need for MAT among pregnant women, given that: a) some women using opioids do not have live births, and b) some neonates exposed to opioids may not experience neonatal abstinence syndrome. However, a portion of the neonates with neonatal abstinence syndrome will do so because their birth mothers accessed MAT (methadone or buprenorphine) during pregnancy.

Cuyahoga County. Available evidence indicates that from 2013 to 2017, there were 629 live-born infants diagnosed with neonatal abstinence syndrome in Cuyhoga County, with 137 infants diagnosed in 2017 alone.[182] I can estimate that at a minimum, approximately 137 women per year in Cuyahoga County need MAT access during their pregnancies. This is an underestimate, however, given that opioid use during pregnancy increases the risk of spontaneous abortion and stillbirth, thus exposed fetuses that progress to live birth are an underestimate of all exposed fetuses. Further, some offspring of women using opioids in pregnancy may not show full clinical neonatal abstinence syndromes. Thus, while the minimum coverage of MAT for women in pregnancy in Cuyahoga County is 137, the total need is likely greater.

Summit County. Available evidence indicates that from 2013 to 2017, there were 426 live-born infants diagnosed with neonatal abstinence syndrome in Summit County, with 71 infants diagnosed in 2017 alone.[182] I can estimate that at a minimum, approximately 71 women per year in Summit County need MAT access during their pregnancies. This is an underestimate, however, given that opioid use during pregnancy increases the risk of spontaneous abortion and stillbirth, thus exposed fetuses that progress to live birth are an underestimate of all exposed fetuses. Further, some offspring of women using opioids in pregnancy may not show full clinical neonatal abstinence syndromes. Thus, while the minimum coverage of MAT for women in pregnancy in Summit County is 71, the total need is likely greater.

F.5 Harm Reduction Interventions: Naloxone distribution.

Harm reduction interventions to reduce overdose mortality as well as health consequences of high-risk modes of drug administration have strong demonstrated efficacy in reducing population burden.

The use of naloxone during an overdose prevents mortality by reversing central nervous system and respiratory depression that occurs after opioid administration. Naloxone is highly effective in reversing the potential fatal consequences of an overdose, and can be administered through numerous sites in the body. In 2015, a nasal spray administration was approved by the FDA which eases administration and reduces potential harm from needle pricks.

Indeed, given the effectiveness of naloxone, the most significant barrier to reducing population health harm is availability of naloxone during an overdose episode. Emergency medical professionals are often the first line of response during an overdose episode, and EMT response times as well as naloxone access vary by county, and by EMT service provider (e.g., Naloxone is less often administered by EMT-basics, who are more common in rural areas). Further, naloxone carrying among police, fire services and other responders is associated with increased overdose reversal.[183,184] Yet disparities remain in the availability of and uptake of naloxone carrying by administrative services that respond to medical events associated with opioid use. Indeed, several studies have documented disparities in naloxone reversal events and opioid overdose events by neighborhood-level and spatial characteristics.[185]

A promising avenue of increased access is bystander naloxone administration and overdose education programs. A review of 41 studies indicated bystander and layperson overdose prevention programs are feasible, that bystanders support training and are willing to administer naloxone, and that such programs reduce overdose.[186] A 2015 meta-analysis of four studies indicated that naloxone administration by bystanders

increased odds of recovery 8.58 times compared to no naloxone administration, and pooled analysis of five studies indicated that trained participants from overdose education programs were more effective for naloxone administration, overdose recognition, and overdose response compared to untrained.[187] Agent-based modeling of naloxone distribution supports the efficacy of kit distribution for reducing overdose deaths.[188] Access to naloxone by bystanders is supported by state laws that expand access, including without needing a prescription.[189] Additionally, many state have adopted "Naloxone Access" or "Good Samaritan" laws that protect bystanders from arrest after reporting an overdose, regardless of whether the bystander is actively using opioids or other drugs.[190] While there have been limited empirical policy evaluations of these laws, an unpublished working paper suggests that states with these laws evidence a reduction in opioid overdose deaths by approximately 8-11%.[191]

In summary, expanding access to naloxone, across first responders to an overdose event as well as bystanders, is an important piece of reducing overdose burden in communities.

F.5.1 Naloxone distribution needs in Cuyahoga County and Summit County

Given that naloxone access is critical to overdose prevention, the question of how many naloxone administration kits would be needed in Cuyahoga and Summit County is important to estimate. There are three categories of individuals who should be given access to naloxone for overdose reversal: a) emergency responders, including EMT, police, and firefighters; b) individuals with opioid use disorder; c) non-using family members of those with opioid use disorder. I estimate the size of these three subsets together in the two counties in order to generate a recommendation of the number of naloxone administration kits that would be minimally necessary per year in each of the counties.

I estimate that the number of individuals who should have access to naloxone includes all regular and/or dependent users of opioids, as well as their families. This estimate is based on public health foundations of prevention and intervention that have been well-described for decades,[192] in that while a small proportion of individuals who are regular and/or dependent users of opioids will die from overdose, prevention and intervention should be available to *all* of those who are at risk. One could view an analogy to prevention of other injury deaths such as vehicle injury. The risk of death due to a car crash per vehicle mile traveled is exceedingly small, but seat belts are available in all vehicles, and mandated for use in almost all states, because all road users are at risk of injury and death. Similarly, all regular and/or dependent users of opioids should have access to life-saving prevention through naloxone, given that there is risk of overdose per use. Further, the consequences of overdose are not minor; hundreds of thousands of lives have been lost due to overdose in the past two decades. Given the severity of the outcome of overdose without interventions such as naloxone, and the foundations of public health that have provided intervention for other injuries, my estimate for the availability and access to naloxone includes all regular and dependent users of opioids as well as their families. The severity of non-fatal overdose as a risk marker for future events is high; indeed, individuals who have a non-fatal overdose are 132.1 times more likely to die in the subsequent year due to a drug-related cause that individuals who do not present with a non-fatal overdose,[153] thus expansive access to naloxone is warranted in order to prevent mortality.

Naloxone administration kits in Cuyahoga County. All first responders should carry naloxone, and intranasal naloxone administration requires minimal training to administer. As of 2015, available data indicated 1,078 individuals on the justice and public safety staff of Cuyahoga County, which would include first responders such as police and fire, although included in that number are both administrative and street staff.[169] This is in addition to medical first responders such as EMS, who are trained to administer naloxone; available data indicate that in 2018, Cuyahoga County EMS administered naloxone at least 4,353 times (this number is likely an underestimate because 81.1% of EMS agencies reported).[193] Further, all regular and opioid dependent individuals should have access to naloxone. As demonstrated in Section C.3., I estimate that there are approximately ~52,000 individuals in Cuyahoga County who are opioid dependent or regular users of opioids. Finally, family members of regular/dependent opioid users should also have access to naloxone.

While the size of the family and social network of individuals in need of naloxone access is not empirically estimable, data from the General Social Survey indicate that the average individual in the US reports four individuals as being their close social network members (including family and friends);[194] therefore, a reasonable estimate is that 220,000 naloxone administration kits are necessary for distribution among the social networks of users. In total, I estimate that Cuyahoga County requires a minimum of 222,000 naloxone administration kits.

Naloxone administration kits in Summit County. All first responders should carry naloxone, and intranasal naloxone administration requires minimal training to administer. Data are not currently available to me regarding the total number of first responders in Summit County, however the Akron Fire department has a current work force of approximately 354 individuals, and there are 14 EMS/paramedics.[195] Available data indicate that in 2018, Summit County EMS administered naloxone at least 1,562 times (this number is likely an underestimate because 81.1% of EMS agencies reported).[193] Further, all regular and opioid dependent individuals should have access to naloxone. In 2018, naloxone distribution in Summit County efforts led to the distribution of 1,680 kits funded by the Depatment of Health that were distributed, and an additional 89 kits distriuted as well. Data from the Depatment of Health indicated that these kits resulted in 454 known overdose reversals, and an additional 1,832 individuals trained to administer naloxone. As demonstrated in Section C.3., I estimate that there are approximately ~11,500 individuals in Summit County who are opioid dependent or regular users of opioids. Finally, family members of regular/dependent opioid users should also have access to naloxone. While the size of the family and social network of individuals in need of naloxone access is not empirically estimable, data from the General Social Survey indicate that the average individual in the US reports four individuals as being their close social network members (including family and friends);[194] therefore, a reasonable estimate is that 58,000 naloxone administration kits are necessary for distribution among the social networks of users. In total, I estimate that Summit County requires a minimum of 58,000 naloxone administration kits.

F.5.3. Routine fentanyl testing at medical facilities and access to fentanyl testing strip for personal use

Among the most devastating trends in the opioid epidemic is the introduction of highly potent fentanyl into the heroin supply in the US. Given that the evidence referenced above has established the causal connections between prescription opioid use and transition to heroin use and the fentanyl-contaminated heroin supply, abatement of the opioid epidemic must include addressing the fatal consequences of fentanyl use in the population.

The need to address fentanyl is underscored by the fact that most users of heroin co-use prescription opioids as well, thus reducing the overdose and other medical consequences of prescription opioid use requires a commitment to fentanyl testing. Data from the Rhode Island Young Adult Prescription Drug Study indicated that between 2015-2016, 11% of non-medical prescription opioid users self-reported also knowingly using fentanyl-contaminated drugs, and that predictors of using fentanyl included diversion of pharmaceutical fentanyl for recreational use, and prescription opioid use to avoid withdrawal, among other predictors.[196]

Fentanyl testing should occur during routine clinical toxicology testing, including at hospitals, emergency departments, clinics and treatment centers. Such testing would necessarily be conducted after potential consumption and injection of fentanyl. Fentanyl testing and feedback to users about exposure promotes awareness of fentanyl exposure and facilitates an opportunity to provide education about harm reduction and overdose prevention. User awareness of fentanyl exposure can also be used to alert others in the users' drug using network about the potential for harm. Finally, data from fentanyl testing can be used for routine surveillance to understand patterns and sources of contamination.[197] Available evidence indicates that fentanyl testing is reliable and valid, and that fentanyl testing information can be routinely collected and shared so that multiple agencies can be alerted.[198–200]

Finally, a promising avenue of harm reduction includes fentanyl test strips that can be directly disseminated to users for testing of heroin and other opioid supply. Available evidence from small studies to date indicates that opioid users are receptive to fentanyl test strips, and that drug use behavior changes when a supply tests positive for fentanyl, either discarding the drug or ensuring that naloxone is available.[201]

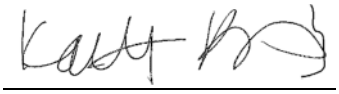
F.5.4. Fentanyl testing needs in Cuyahoga County and Summit County

Available evidence indicates that fentanyl testing should occur during clinical toxicology testing at hospitals, emergency departments, clinics and treatment centers. Further, users themselves should have access to fentanyl test strips for personal use of their drug supply.

Similar to the reasons above regarding the need for naloxone access for regular and/or dependent users of opioids, there is a public health need and justification for fentanyl test strips availability for all users. Given the severe consequences of the risk of overdose using fentanyl and fentanyl-contaminated heroin and prescription opioids, it is essential to provide access to test strips at a broad level that ensures access to all regular and/or dependent users.

Fentanyl testing needs in Cuyahoga County. In 2017, emergency departments in Cuyahoga treated an estimated 9,191 patients with drug-related injuries, an average of 25 per day.[202] This is a 21% increased from 2016, and the groups at highest risk are 35-49 year old men.[203] Data on the proportion of these visits that are attributable to opioids is not available for all visits; of those records with information on opioids, selected prescription drugs and selected other drugs (available for 2,529 of the 9,191 visits), the available data indicate that there are at least 7 visits per day in Cuyahoga County emergency departments related to opioid use. Further, users should have access to fentanyl test strips for personal use. Given that there are an estimated ~52,300 individuals in Cuyahoga County who are opioid dependent or regular users of opioids, using at least daily, I would estimate that 19 million fentanyl test strips (52,300 x 365 days) would be needed per year to provide enough information for users to avoid harm, with additional test strips needed for emergency department use of at least 2,555 per year.

Fentanyl testing needs in Summit County. In 2018, there were an estimated 1,507 admissions to emergency departments and hospitals in Summit County for drug overdose, and a total of 178,234 admissions total since 2012.[204] Available data do not allow for the assessment of the proportion of these overdoses that were due to opioids. However, these estimates are still a lower bound, given that there may be admissions for opioid-related reasons that do not involve drug overdose (e.g. pneumonia). Further, users should have access to fentanyl test strips for personal use. Given that there are an estimated 11,500 individuals in Sumit County who are opioid dependent or regular users of opioids, using at least daily, I would estimate that 4.2 million fentanyl test strips would be needed per year to provide enough information for users to avoid harm, with an additional 1,500 test strips needed for emergency department use.

Submitted By: 

March 24, 2019

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202. Drug-related emergency room visits, January 1-December 31, 2017. Data Brief: Annual Report, Cuyahoga County Board of Health. http://www.ccbh.net/wp-content/uploads/2018/02/Epi-Center-Drug-Related-Injuries-Report-Annual-Report-2017-2.12.18.pdf. Published 2017.
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Fee Schedule for Katherine M. Keyes, Ph.D., MPH

Attachment to Expert Report, Dated March 25, 2019

In the National Prescription Opioid Litigation, MDL 2804, Katherine M. Keyes, Ph.D., MPH, compensation for time spent reviewing materials and writing her Expert Report is $400.00 per hour, and $550.00 per hour for deposition and trial testimony.

DATE OF PREPARATION OF CV: DECEMBER 18, 2018

PERSONAL DATA

Katherine M. Keyes PhD MPH
Birth date: April 8th, 1980
Birthplace: Minneapolis, MN
Citizenship: USA

Institutional affiliation:

Department of Epidemiology
Columbia University
722 West 168th Street
New York, NY 10032
Phone: (212) 305-6706
Fax: (212) 305-9413
Email: kmk2104@columbia.edu

ACADEMIC TRAINING

University of Minnesota — September 1998 – December 2001
Bachelor of Science, with Honors — Minneapolis, MN
Bachelor of Arts, with Honors

Columbia University — September 2004 – May 2006
Master of Public Health, Epidemiology — New York, NY

Columbia University — September 2006 – June 2010
Doctor of Philosophy, Epidemiology — New York, NY
Thesis title: Ecologic-level disapproval and the prevalence of substance use: A multi-level age-period-cohort analysis of high-school attending adolescents in the United States.
Sponsor: Deborah Hasin
Publications: see peer-reviewed journal publications #45, 51, and 65.

ACADEMIC APPOINTMENTS

Associate Professor of Epidemiology — July 2016-Present
Department of Epidemiology — New York, NY
Columbia University Mailman School of Public Health

Assistant Professor of Epidemiology — February 2012-June 2016
Department of Epidemiology — New York, NY
Columbia University Mailman School of Public Health

Assistant Professor of Epidemiology (in Psychiatry) — January 2013-July 2016
Department of Psychiatry — New York, NY
Columbia University College of Physicians and Surgeons

Adjunct Research Assistant Professor — January 2015-present
Survey Research Center, Institute for Social Research — Ann Arbor, MI
University of Michigan

Adjunct Associate Professor — July 2018-present
Society and Health Research Center — Santiago, Chile
Universidad Mayor

TRAINEESHIPS

Columbia University, New York, NY — June 2010 – January 2012
Columbia University Epidemiology Merit Post-doctoral Fellow

Columbia University, New York, NY — Sept 2006 – June 2010
Psychiatric Epidemiology Pre-doctoral Training Fellow (T32 MH013043, PI: Link)

PROFESSIONAL ORANIZATIONS AND SOCIETIES

American Psychopathological Association (2006-present)
- *Nominations committee, 2013
- * Robins-Guze early career investigator award recipient, 2017

Research Society on Alcoholism (2006-present)
- * Program committee, 2015-2017
- * Young Investigator Award recipient, 2015

Society for Epidemiologic Research (2007-present)
- * Lilienfeld award recipient, 2008
- * Education committee, 2015-present
- * Member-at-Large, Executive committee, 2018-present

Society for Research on Child Development (2012-present)
- * Thornberg Dissertation Award committee, 2014-2018
- * Communications committee, 2017-present

World Psychiatric Association Epidemiology and Public Health Section (2011-present)
- *Michelle Tansella Award recipient, 2016
- *Executive committee, 2016-present
- *Local host of 2018 meeting, held at Columbia University, New York, May 2-4th, 2018

SELECTED HONORS AND AWARDS

Student Merit Travel Award, Research Society on Alcoholism, 2006
Women & Gender Junior Investigator Award, College on Problems of Drug Dependence, 2006
Finalist, Gordis Award for outstanding student research, Research Society on Alcoholism, 2007
Student Merit Travel Award, Research Society on Alcoholism, 2007
Lilienfeld Prize for Student Research, Society for Epidemiologic Research, 2008
Gordis Award for outstanding student research, Research Society on Alcoholism, 2008
Student Merit Travel Award, Research Society on Alcoholism, 2008
National Institute of Drug Abuse Travel Award, American Psychological Association, 2009
First place, Division 50 Student Poster Competition, American Psychological Association, 2009
Student award, Epidemiology Section, American Public Health Association, 2009
Student Merit Travel Award, Research Society on Alcoholism, 2009
William Farr Award in Epidemiology, Columbia University, 2010
Robert Wood Johnson Health and Society Scholars Fellowship, 2010 (declined)
Columbia Psychiatric-Neurological Epidemiology Early Investigator Award, 2012
Research Society on Alcoholism Young Investigator Award, 2015
Tow Scholarship, Mailman School of Public Health, Columbia University, 2015
Calerdone Junior Faculty Prize, Mailman School of Public Health, Columbia University, 2016

Michelle Tansella Award, World Psychiatric Association Epidemiology section, 2016
Robins-Guze early career investigator award, American Psychopathological Association, 2016
NIH Early-Stage Investigator, Office of Disease Prevention, 2017

FELLOWSHIP AND GRANT SUPPORT

PENDING

"As adolescent substance use declines, internalizing symptoms increase: identifying high-risk substance using groups and the role of social media, parental supervision, and unsupervised time" (PI: Keyes)
Grant number TBA
Role on project: Principal investigator
Dates of funding: 07/01/2019-06/30/2024
Funder: National Institute of Drug Abuse (R01 submission)
Total direct and indirect costs: $434,794
To be reviewed March 2019

"Health aging with alcohol? Harnessing longitudinal data from 20 countries to understand health impacts of moderate drinking among older adults" (PI: Keyes)
R01-AA026959
Role on project: Principal investigator
Dates of funding: 04/01/2019-03/31/2024
Funder: National Institute of Alcohol Abuse and Alcoholism (R01 submission)
Total direct and indirect costs: $485,851.00
To be reviewed May 2019

"Diverging trends between depression/suicidality and alcohol/opioid use among adolescents in the United States: Subgroup variation and the role of social media in 2 samples of adolescents" (PI: Keyes)
Grant number TBA, subproject of CDC injury center resubmission
Role on project: Principal investigator
Dates of funding: 07/01/2019-06/30/2021
Funder: Centers for Disease Control and Prevention
Total direct and indirect costs: $200,000
Score: 19 (percentile unavailable)
Pending final funding decision

"Examining the synergistic effects of cannabis and prescription opioid policies on chronic pain, opioid prescribing, and opioid overdose" (PI: Martins and Cerda)
Role on project: Co-Investigator
Funder: National Institute on Drug Abuse (R01 submission)
Currently pending funding

PRESENT

"Columbia Injury Control Research Center" (PI: Li)
R49 CE002096
Role on project: Research Director
Dates of funding: 08/01/2012-07/31/2019

Funder: Centers for Disease Control and Prevention

"Age, period, and cohort effects on gender differences in alcohol use and alcohol-related problems in 47 national, longitudinally-followed cohorts" (PI: Keyes and Jager)
R01-AA026861
Role on project: Principal investigator and contact PI (Multiple PI with Justin Jager)
Dates of funding: 07/01/2018-06/30/2023
Funder: National Institute of Alcohol Abuse and Alcoholism
Total direct and indirect costs: $529,899

"Substance abuse history, mental health and firearm violence: from evidence to action" (PI: Keyes and Cerda)
Role on project: Principal investigator and Contact PI (Multiple PI with Magdalena Cerda)
Dates of funding: June 2015 – May 2019 (currently on NCE)
Funder: National Institute of Alcohol Abuse and Alcoholism (R21 DA041154)
Direct costs: $275,000

"Race, alcohol consumption, and vehicle crashes: an epidemiologic paradox" (PI: Keyes)
Role on project: Principal investigator
Dates of funding: June 2013 – May 2019 (currently on NCE)
Funder: National Institute of Alcohol Abuse and Alcoholism (K01AA021511)
Direct costs: $849,849

"Aging well with alcohol? Harnessing longitudinal data from 20 countries to understand health impacts of moderate drinking among older adults" (PI: Keyes)
Role on project: Principal investigator
Dates of funding: June 2017 – May 2019
Funder: The Robert N. Butler Columbia Aging Center
Direct costs: $30,000

"Drug use among nightclub and dance festival attendees in New York City" (PI: Palamar)
Role on project: Co-Investigator, PI of Columbia subcontract
Dates of funding: 09/01/2018-05/31/2021
Funder: National Institute on Drug Abuse (R01-DA044207)
Total direct and indirect costs: $497,339

"**Monitoring the Future: Drug Use and Lifestyles of American Youth**" (PI: Miech)
Role on project: Co-Investigator, PI of Columbia subcontract
Dates of funding: August 2017 – June 2022
Funder: National Institute on Drug Abuse (R01 DA001411)
Direct costs: $5,123,733

"State medical marijuana laws and NSDUH marijuana use and consequences since 2004" (PI: Martins)
Role on project: Co-Investigator
Dates of funding: August 2013 – December 2018 (currently on NCE)
Funder: National Institute on Drug Abuse (R01 DA037866)
Direct costs: $ 750,000

PAST

"State medical marijuana laws and teen marijuana use and attitudes since 1991" (PI: Hasin)
Role on project: Co-Investigator, PI of Columbia subcontract
Dates of funding: August 2012 – July 2017
Funder: National Institute on Drug Abuse (R01 DA034244)
Direct costs: $ 374,562

"Neighborhood interventions in alcohol-related homicide: a systems approach" (MPI: Keyes and Cerda)
Role on project: Principal investigator and Contact PI (Multiple PI with Magdalena Cerda)
Dates of funding: October 2013-September 2016
Funder: National Institute of Alcohol Abuse and Alcoholism (R21 AA021909)
Direct costs: $275,000

"Racial/Ethnic Disparity in Alcohol-Attributable Mortality from Motor Vehicle Crashes"
Role on project: Principal investigator (PI)
Dates of funding: January 2016 – December 2016
Funder: Columbia University Center for Injury Epidemiology and Prevention
Direct costs: $10,000

"Correcting nonresponse bias in national surveys"
Role on project: Principal investigator
Dates of funding: November 2015-October 2016
Funder: Columbia University Calderone Junior Faculty Prize
Direct costs: $25,000

"Principles of Epidemiology: a flipped classroom proposal"
Role on the project: Principal Investigator (Multiple PI with Silvia Martins)
Dates of funding: May 2015 to May 2016
Funder: Columbia University Provost Hybrid Learning Course Redesign and Delivery program
Direct costs: $12,000

"Mental health and firearm violence: from evidence to action (MPI: Keyes and Cerda)
Role on project: Principal investigator (Multiple PI with Magdalena Cerda)
Dates of funding: January 2015 – December 2015
Funder: Columbia University Center for Injury Epidemiology and Prevention
Direct costs: $10,000

"Developing a translational framework for studying grief and grief-related pathologies"
Role on the project: Co-Investigator (PI: Zoe Donaldson)
Dates of funding: May 2015 – September 2015
Funder: Columbia University Collaborative and Multidisciplinary Pilot Research Awards
Direct costs: $15,000

"**Does structural discrimination explain health disparities by race? Preliminary analyses in state-to-state mobility**" (PI: Keyes)
Role on project: Principal investigator
Dates of funding: December 2012 – June 2013
Funder: Robert Wood Johnson Health & Society Scholars Program at Columbia University
Direct costs: $5,000.00

Research Associate Award: "The longitudinal emergence of racial/ethnic differences in alcohol use disorders and depression from adolescence to adulthood" (PI: Keyes)
Role on project: Principal Investigator
Dates of funding: September 2011 – June 2012
Funder: Columbia University
Direct costs: $30,000.00.

"Period and cohort effects in adolescent substance use: testing the effects of the social environment in a time series of U.S. adolescents from 1976-2008" (PI: Keyes)
Role on project: Principal Investigator
Dates of funding: December 2010 – June 2011
Funder: Robert Wood Johnson Health & Society Scholars Program at Columbia University
Direct costs: $10,000.00

"Age-period-cohort effects on substance use in adolescence, 1976-2006" (PI: Keyes)
Role on project: Principal Investigator
Dates of funding: June 2009 – October 2011 (electively terminated June 2010 due to early graduation)
Funder: National Institute on Drug Abuse (F31 DA026689-01)

TEACHING EXPERIENCE AND RESPONSIBILITIES

Role: Instructor

- EPID P8410: *Psychiatric Epidemiology*, 2016-2017
- HPMN P8545: *Analysis of Large-Scale Data*, 2016-2018
- EPIC Summer Institute: *Principles of Epidemiology*, 2014-2018
- EPIC Summer Institute: *Multi-level analysis for public health research*, 2016-2018
- EPID 787: *Multi-level analysis for public health research*, 2015-2018 (University of Michigan Graduate Summer Session in Epidemiology)
- Special short course: *Multi-level analysis for public health research*, 2017, (University of Cape Town, Cape Town, South Africa)
- EPID P6400: *Principles of Epidemiology*, 2010- 2015
- EPIC Summer Institute: *Analysis of Complex Survey Data*, 2011-2013
- MSPH Core: *Quantitative Foundations of Public Health*, 2012

Role: Assistant Course Director

- EPID P6400: *Principles of Epidemiology*, 2008, 2009

Role: Guest lecturer

- K Award Seminar Series, New York State Psychiatric Institute, 2013-2018
- EPID P9489: *Advanced Techniques in Epidemiological Methods*, 2017
- MPH Core Module 202-206: *Principles of Epidemiology*, (École des hautes études en santé publique, Paris, France), 2011-2016
- EPID P8416: *Selected Problems in Measurement*, 2010-2016
- EPID P8438: *Design and Conduct of Observational Epidemiology*, 2012-2015
- EPID P8419: *Reading Seminar in Psychiatric Epidemiology*, 2009-2015
- EPID P8470: *Epidemiology of Alcohol and Drug Problems*, 2011-2015

- EPID P9419: *Master's Essay in Epidemiology*, 2008-2015
- EPID P8471: *Social Epidemiology*, 2010

Role: Teaching assistant

- EPID P6400: *Principles of Epidemiology*, 2006-2008
- EPID P8421: *Introduction to Clinical Psychiatry for Public Health*, 2006
- EPID P8471: *Social Epidemiology*, 2008
- EPID P8419: *Reading Seminar in Psychiatric Epidemiology*, 2009
- EPID P8470: *Epidemiology of Alcohol and Drug Problems*, 2010

TRAINING PROGRAM INVOLVEMENT

T32 MH013043-45 "A Research Training Program in Psychiatric Epidemiology"
Role: Co-Director (with Ezra Susser, Bruce Dohrenwend, and Sharon Schwartz)

T32 DA-031099-05 "Epidemiology of Substance Use Disorders Training Program at Columbia University" (PI: Hasin)
Role: Faculty, Steering Committee

T32 ES023772-02 "Training Program in Environmental Life Course Epidemiology" (PI: Factor-Litvak
Role: Faculty

DEPARTMENTAL SERVICE

- Faculty director, Executive MS in Epidemiology Program, 2012-2015
- Methods qualifying exam committee, 2015-present

STUDENT ADVISEES

Master's students:

Mary Elizabeth Smith, 2011 (thesis, second reader)
Pedro Carneiro, 2012 (thesis, second reader)
Bryan Kutner, 2012 (thesis, second reader)
Erin Gilbert, 2012 (thesis, second reader)
Xinfan Liu, 2012 (thesis, second reader)
Charissa Pratt, 2013 (thesis, first reader)
Arti Virkud, 2013 (thesis, first reader)
Jonathan Platt, 2013 (thesis, first reader)
Edward Gastel, 2013 (thesis, first reader)
Nathalie DuRivage, 2013 (thesis, first reader)
Thomas Vo, 2014 (thesis, first reader)
Mark Morgan, 2014 (thesis, first reader)
Sabrina Cheng, 2014 (thesis, first reader)
Stephanie Brazis, 2014 (thesis, first reader)
Ruth Chang, 2014 (thesis, first reader)
Amy Lanza, 2015 (thesis, first reader)
David Sowa, 2015 (thesis, first reader)
Chidinma Egbukichi, 2015 (thesis, first reader)

Khudejha Asghar, 2015 (thesis, first reader)
Dahsan Gary, 2016 (thesis, first reader)
Joy Ukaigwe, 2016 (thesis, first reader)
Elizabeth Wartella, 2016 (thesis, first reader)
Rachel Webster, 2016 (thesis, first reader)
Caroline Hugh, 2017 (thesis, first reader)
Ghadah Gadi, 2017 (thesis, first reader)
Margaret Havunjian, 2018 (thesis, first reader)
Miriam Woodward, 2018 (thesis, first reader)
Ian Rodgers, 2018 (thesis, first reader)
Tatini Mal-Sarkar, expected 2019 (thesis, first reader)
Noah Kreski, expected 2019 (thesis, first reader)
Mia Pandit, expected 2019 (thesis, first reader)

Doctoral students (former):

Joanne Brady, 2013-2014 (dissertation, second reader)
*Currently: senior research fellow, NORC at the University of Chicago
Melissa Dupont-Reyes, 2015-2017 (dissertation, second reader)
*Currently: post-doctoral fellow, University of Texas at Austin, Latino Research Initiative
Nina Banerjee, 2014-present (dissertation, second reader)
* Currently: psychologist in private practice, Orange County, CA
Julian Santaella, 2015-2018 (dissertation, sponsor)
*Currently: faculty, Universidad del Valle, Colombia

Doctoral students (present):

Paula Bordelois, 2015-present (dissertation, sponsor)
Jonathan Platt, 2015-present (dissertation, sponsor)
Somjen Frazer, 2015-present (dissertation, outside reader)
David Fink, 2015-present (dissertation, second reader)
Aravind Pillai, 2016-present (dissertation, second reader)
Victor Puac-Polanco, 2018-present (dissertation, chair)
Greg Cohen, 2018-present (dissertation, chair)
Eleanor Hayes-Larson, 2018-present (dissertation, second reader)

Discussant for dissertation proposal defense:

Wendy Cheng, 2014
Kate Sapra, 2014
Emily Greene, 2016

OTHER PROFESSIONAL ACTIVITIES

JOURNAL EDITING

Current

- Drug and Alcohol Dependence, Associate Editor, 2015 to present
- American Journal of Public Health, guest editor, Special Section: "Improving Population Mental Health in the 21st Century", 2018
- Alcoholism: Clinical and Experimental Research, Field Editor, 2014 to present
- Injury Epidemiology, Associate Editor, 2013 to present

Former

- BMC Psychiatry, Associate Editor, 2011 to 2015
- Social Psychiatry and Psychiatric Epidemiology, Editor of commentaries and editorials, 2014 to 2016

JOURNAL REVIEW (SELECTION)

Addiction; Alcoholism: Clinical and Experimental Research; American Journal of Epidemiology; American Journal of Psychiatry; American Journal of Public Health; Archives of General Psychiatry; BMC Psychiatry; British Journal of Psychiatry; Contemporary Drug Problems; Demography; Depression and Anxiety; Drug and Alcohol Dependence; Epidemiology; International Gambling Studies; International Journal of Epidemiology; JAMA; JAMA Pediatrics; JAMA Psychiatry; Journal of Nervous and Mental Diseases; Journal of Psychiatric Research; Journal of Traumatic Stress; Journal of Studies on Alcohol and Drugs; Molecular Psychiatry; New England Journal of Medicine; Preventive Medicine; PLoS One; Psychological Medicine; Social Psychiatry and Psychiatric Epidemiology; Social Science and Medicine; Substance Abuse Treatment, Prevention, and Policy

ABSTRACT REVIEW

Society for Epidemiologic Research

NIH STUDY SECTIONS

- NIAAA: AA1: Biomedical Research Review Subcommittee, November 9th, 2015
- NIAAA: AA1: Biomedical Research Review Subcommittee, July 11th, 2016
- NIDA: Special Emphasis Panel: PAR-16-24: Accelerating the Pace of Drug Abuse Research Using Existing Data, November 4th, 2016
- NIAAA: AA2: Epidemiology, Prevention and Behavior Research Review Subcommittee, March 6th, 2017
- Social Sciences and Population Studies-B (SSPB) study section, June 15th, 2017
- NIAAA: AA1: Biomedical Research Review Subcommittee, July 14th, 2017
- NIAAA: AA2: Epidemiology, Prevention and Behavior Research Review Subcommittee, March 5th, 2018
- NIDA: Special Emphasis Panel: PAR-16-24: Accelerating the Pace of Drug Abuse Research Using Existing Data, March 1st, 2018

NATIONAL COMMITTEE MEMERSHIP

National Academy of Sciences, Engineering, and Medicine: Health and Medicine Division
"Accelerating the Progress to Reduce Alcohol-Impaired Driving Fatalities"
In progress, 2017-2018

PUBLICATIONS

PEER-REVIEWED JOURNAL PUBLICATIONS

1. Hasin DS, Hatzenbuehler ML, **Keyes KM,** Ogburn E. 2006. Substance use disorders: Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and International Classification of Diseases, tenth edition (ICD-10). Addiction, (101 Suppl 1): 59-75. PMID: 16930162.

2. Hasin DS, **Keyes KM**, Hatzenbuehler M, Aharonovich E, Alderson D. 2007. Effects of physical proximity, loss, and previously-assessed history on alcohol use and traumatic stress symptoms following terrorist attacks. American Journal of Public Health, 97(12):2268-75. PMID: 17971553. PMCID: PMC2089108.

3. Goodwin RD, **Keyes KM**, Simuro N. 2007. Cigarette use and mental disorders during pregnancy. American Journal of Obstetrics and Gynecology, 109(4):875-83. PMID: 17400849.

4. Goodwin RD, Zvolensky, MJ, **Keyes KM**. 2008. Nicotine dependence and mental disorders among adults in the United States. Evaluating the role of mode of administration. Psychological Medicine, 43(3):1471-1477. PMID: 18366824.

5. **Keyes KM**, Hatzenbuehler ML, Alberti PM, Narrow WE, Grant BF, Hasin DS. 2008. Service utilization differences for axis I psychiatric and substance use disorders between white and black adults. Psychiatric Services, 59(8):893-901. PMID: 18678687. PMCID: PMC2729457.

6. Beseler C, Aharonvich E, **Keyes KM**, Hasin DS. 2008. Adult transition from at-risk drinking to alcohol dependence: The relationship of family history and drinking motives. Alcoholism: Clinical and Experimental Research, 32(4):607-16. PMID: 18341650. PMCID: PMC3850293.

7. Heiman G, Ogburn E, Gorroochurn P, **Keyes KM**, Hasin D. 2008. Evidence for a two-stage model of dependence using the NESARC and its implications for genetic association studies. Drug and Alcohol Dependence, 92(1-3), 258-266. PMID: 17933473. PMCID: PMC2266584.

8. **Keyes KM,** Martins SS, Hasin DS. 2008. Past 12-month and lifetime comorbidity and poly-drug use of ecstasy users among young adults in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug and Alcohol Dependence, 97(1-2): 139-149. PMID: 18524499. PMCID: PMC3771490.

9. Vesga-Lopez O, Blanco C, **Keyes KM**, Olfson M, Grant BF, Hasin DS. 2008. Psychiatric disorders in pregnant and postpartum women in the United States. Archives of General Psychiatry, 65(7):805-15. PMID: 18606953. PMCID: PMC2669282.

10. Hatzenbuehler ML, **Keyes KM**, Narrow WE, Grant BF, Hasin DS. 2008. Racial/Ethnic disparities in service utilization for mental health and substance disorders: comorbid individuals in the general population. Journal of Clinical Psychiatry, 69(7):1112-1121. PMID: 18517286. PMCID: PMC2745048.

11. **Keyes KM**, Hasin DS. 2008. Socio-economic status and problem alcohol use: the positive relationship between income and the DSM-IV alcohol abuse diagnosis. Addiction, 103(7):1120-30. PMID: 18494841. PMCID: PMC385924.

12. Thompson R, Lizardi D, **Keyes KM,** Hasin DS. 2008. Childhood or Adolescent Parental Divorce/Separation, Parental History of Alcohol Problems, and Offspring Lifetime Alcohol Dependence. Drug and Alcohol Dependence, 98(3):264-269. PMID: 18757141. PMCID: PMC3818521.

13. **Keyes KM**, Grant BF, Hasin DS. 2008. Evidence for a closing gender gap in alcohol use, abuse, and dependence in the United States population. Drug and Alcohol Dependence, 93(1-2): 21-29. PMID: 17980512. PMCID: PMC3163892.

14. Hasin D, **Keyes KM**, Alderson D, Wang S, Aharonovich E, Grant B. 2008. Cannabis withdrawal in the United States: Results from the NESARC. Journal of Clinical Psychiatry, 69(9);1354-63. PMID: 19012815. PMCID: PMC2777674.

15. Goodwin R, Davidson KW, **Keyes KM**. 2009. Mental disorders and cardiovascular disease among adults in the United States. Journal of Psychiatric Research, 43(3): 239-246. PMID: 18614179. PMCID: PMC3340909.

16. Hatzenbuehler ML, **Keyes KM,** Hasin DS. 2009. Associations between perceived weight discrimination and the prevalence of psychiatric disorders in the general population. Obesity, 17(11):2033-2039. PMID: 19390520. PMCID: PMC3767420.

17. Goodwin, RD, **Keyes KM**, Hasin DS. 2009. Changes in cigarette use and nicotine dependence in the United States. American Journal of Public Health, 99(8):1471-1477. PMID: 19008515. PMCID: PMC2707489.

18. Pilowsky D, **Keyes KM**, Hasin DS. 2009. Adverse Childhood Events and Lifetime Alcohol Dependence. American Journal of Public Health, 99(2):258-263. PMID: 19059847. PMCID: PMC2622772.

19. Goodwin RD, **Keyes KM**, Stein MB, Talley NJ. 2009. Peptic ulcer and mental disorders among adults in the community: The role of nicotine and alcohol use disorders. Psychosomatic Medicine, 71(4)463-468. PMID: 19443694. PMCID: PMC3340907.

20. Martins SS, **Keyes KM,** Storr CL, Zhu H, Chilcoat, HD. 2009. Pathways between nonmedical opioid use/dependence and psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug and Alcohol Dependence, 103(1-2):16-24. PMID: 19414225. PMCID: PMC2699563.

21. **Keyes KM,** Geier T, Grant BF, Hasin DS. 2009. Influence of a drinking quantity and frequency measure on the prevalence and demographic correlates of DSM-IV alcohol dependence. Alcoholism: Clinical and Experimental Research, 33(5):761-771. PMID: 19298332. PMCID: PMC3163446.

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23. Hatzenbuehler ML, **Keyes KM,** Hasin DS. 2009. State-level policies and psychiatric morbidity in lesbian, gay, and bisexual populations. American Journal of Public Health, 99(12):2275-2281. PMID: 19833997. PMCID: PMC2775762.

24. Hatzenbuehler ML, McLaughlin K, **Keyes KM**. The impact of institutional discrimination on psychiatric disorders in lesbian, gay, and bisexual populations: a prospective study. 2010. American Journal of Public Health, 100(3):452-459. PMID: 20075314. PMCID: PMC2820062.

25. Baca-Garcia E, Perez-Rodriguez M, **Keyes KM**, Oquendo MA, Hasin DS, Grant BF, Blanco C. 2010. Suicidal ideation and suicide attempts in the United States: 1991-1992 and 2001-2002. Molecular Psychiatry, 15(3):250-259. PMID: 18779820. PMCID: PMC2825279.

26. **Keyes KM,** Utz R, Robinson W, Li G. 2010. What is a cohort effect? Comparison of three statistical methods for modeling cohort effects in obesity prevalence in the United States, 1971–2006. Social Science and Medicine, 70:1100-1108. PMID: 20122771. PMCID: PMC3469580.

27. McLaughlin K, Hatzenbuehler M, **Keyes KM.** 2010. Responses to Discrimination and Psychiatric Disorders Among Black, Hispanic, Female, and Lesbian, Gay, and Bisexual Individuals. American Journal of Public Health, 100(8):1477-1484. PMID: 20558791. PMCID: PMC2901295.

28. Martins SS, **Keyes KM**, Storr CL, Zhu H, Grucza, RA. 2010. Birth-Cohort Trends in Lifetime and Past-Year Prescription Opioid-Use Disorder Resulting From Nonmedical Use: Results From Two National Surveys. Journal of Studies on Alcohol and Drugs, 71(4)480-487. PMID: 20553656. PMCID: PMC2887918.

29. Shmulewitz D, **Keyes KM**, Beseler C, Aharonovich E, Aivadyan C, Spivak B, Hasin DS. 2010. The dimensionality of alcohol use disorders: Results from Israel. Drug and Alcohol Dependence, 111(1-2):146-154. PMID: 20537809. PMCID: PMC3884677.

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32. **Keyes KM**, Li G. 2010. A multi-phase method for estimating cohort effects in age-period contingency table data. Annals of Epidemiology, 20(10):779-785. PMID: 20627769. PMCID: PMC2946643.

33. Lizardi D, Thompson R, **Keyes KM**, Hasin DS. 2010. The role of depression in the differential effect of childhood parental divorces on male and female adult offspring suicide attempt risk. Journal of Nervous and Mental Diseases, 198(9):687-690. PMID: 20823733. PMCID: PMC3755764.

34. **Keyes KM**, Hatzenbuehler ML, McLaughlin K, Link BG, Olfson M, Grant B, Hasin DS. 2010. Stigma and treatment for alcohol disorders in the United States. American Journal of Epidemiology, 172(12):1364-1372. PMID: 21044992. PMCID: PMC2998202.

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36. **Keyes KM,** Keyes MA, March D, Susser E. 2011. Levels of risk: maternal-, middle childhood-, and neighborhood-level predictors of adolescent disinhibitory behaviors from a longitudinal birth cohort in the United States. Mental Health and Substance Use, 4(1):22-37. PMID: 21483643. PMCID: PMC3072573.

37. Eaton N**,** Krueger RF, **Keyes KM**, Skodol A, Markon K, Grant B, Hasin D. 2011. Borderline Personality Disorder Comorbidity: relationship to the internalizing-externalizing structure of common mental disorders. Psychological Medicine, 41(5):1041-1050. PMID: 20836905. PMCID: PMC3193799.

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39. Skodol AE, Grilo CM, **Keyes KM**, Geier T, Grant BF, Hasin DS. 2011. Relationship of Personality Disorders to the Course of Major Depressive Disorder in a Nationally Representative Sample. American Journal of Psychiatry, 168(3):257-264. PMID: 21245088. PMCID: PMC3202962.

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41. **Keyes KM**, Martins S, Hatzenbuehler ML, Bates L, Blanco C, Hasin DS. 2011. Mental health service utilization for psychiatric disorders among Latinos living in the United States: the role of ethnic subgroup, ethnic identity, and language/social preferences. Social Psychiatry and Psychiatric Epidemiology. Epub Feb 3. PMID: 21290097. PMCID: PMC3756540.

42. Hatzenbuehler ML, **Keyes KM,** McLaughlin K. 2011. The protective effects of social/contextual factors on psychiatric morbidity in LGB populations. International Journal of Epidemiology, 40(4)1071-80. PMID: 21330343. PMCID: PMC3156367.

43. Goodwin RD, Lipsitz JD, **Keyes KM,** Galea S, Fyer AJ. 2011. Family history of alcohol use disorders among adults with panic disorder in the community. Journal of Psychiatric Research, 45(8)1123-7. PMID: 21334007. PMCID: PMC3337757.

44. **Keyes KM**, Hatzenbuehler ML, Hasin DS. 2011. Stressful life experiences, alcohol consumption, and alcohol use disorders: the epidemiologic evidence for four main types of stressors. Psychopharmacology, 218(1):1-17. PMID: 21373787. PMCID: PMC3755727.

45. **Keyes KM**, Schulenberg JS, O'Malley PE, Johnston LD, Bachman JG, Li G, Hasin DS. 2011. The social norms of birth cohorts and adolescent marijuana use in the United States, 1976–2007. Addiction, EPub May 6. PMID: 21545669. PMCID: PMC3174352.

46. Shmulewitz D, **Keyes KM**, Wall MM, Aharonovich E, Aivadyan C, Greenstein E, Spivak B, Weizman A, Frisch A, Grant BF, Hasin DS. 2011. Nicotine dependence, abuse and craving: dimensionality in an Israeli sample. Addiction, 106(9):1675-86. PMID: 21545668. PMCID: PMC3163441.

47. Hatzenbuehler ML, Wieringa NF, **Keyes KM**. 2011. Community-level determinants of tobacco use disparities in LGB youth: Results from a population-based study. Archives of Pediatrics and Adolescent Medicine, 165(6): 527-32. PMID: 21646585.

48. Baca-Garcia E, Perez-Rodriguez MM, Oquendo MA, **Keyes KM**, Hasin DS, Grant BF, Blanco C. Estimating risk for suicide attempt: are we asking the right questions? Passive suicidal ideation as a marker for suicidal behavior. Journal of Affective Disorders, EPub Jul 22. PMID: 21784532. PMCID: PMC3172880.

49. Wall M, Poh E, Cerda M, **Keyes KM**, Galea S, Hasin DS. 2011. Adolescent marijuana use from 2002 to 2008: higher in states with medical marijuana laws, cause still unclear. Annals of Epidemiology, 21(9):714-716. PMID: 21820632. PMCID: PMC3358137.

50. Eaton, NR, **Keyes KM**, Krueger, RF, Balsis S, Skodol AE, Markon KE, Grant BF, Hasin DS. 2011. An Invariant Dimensional Liability Model of Gender Differences in Mental Disorder Prevalence: Evidence from a National Sample. Journal of Abnormal Psychology, Aug 15 EPub. PMID: 21842958. PMCID: PMC3402021.

51. **Keyes KM**, Li G, Hasin DS. 2011. Birth cohort effects and gender differences in alcohol epidemiology: a review and synthesis. Alcoholism: Clinical and Experimental Research, 35(12):2101-2012. PMID: 21919918. PMCID: PMC3221910.

52. Lee SY, Martins SM, **Keyes KM**, Lee HB. 2011. Mental Health Service Use by Persons of Asian Ancestry With DSM-IV Mental Disorders in the United States. Psychiatric Services, 62(10): 1180-6. PMID: 21969644. PMCID: PMC3698479.

53. **Keyes KM**, Liu XC, Cerda M. 2011. The role of race/ethnicity in alcohol-attributable injury in the United States. Epidemiologic Reviews, ePub Sep 19. PMID: 21930592. PMCID: PMC3283099.

54. Martins SS, Fenton MC, **Keyes KM**, Blanco C, Zhu H, Storr CL. 2011. Mood/Anxiety disorders and their association with non-medical prescription opioid use and prescription opioid use disorder: longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions. Psychological Medicine, ePub Oct 17. PMID: 21999943. PMCID: PMC3513363.

55. Hankerson SH, Fenton MC, Geier TJ, **Keyes KM**, Weissman MM, Hasin DS. 2011. Racial Differences in Symptoms, Comorbidity, and Treatment for Major Depressive Disorder among Black and White Adults. Journal of the National Medical Association, 103(7):576-84. PMID: 21999032. PMCID: PMC3866690.

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57. Hasin DS, Fenton M, Skodal A, Krueger R, **Keyes KM**, Blanco C, Johnson J, Geier T, Grant B. 2011. Personality disorders and the 3-year course of alcohol, drug, and nicotine use disorders. Archives of General Psychiatry, 68(11):1158-1167. PMID: 22065531. PMCID: PMC3500879.

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62. Cerda M, Wall M, **Keyes KM**, Galea S, Hasin DS. 2012. Medical marijuana laws in 50 states: investigating the impact of state legalization of medical marijuana and marijuana use, abuse and dependence. Drug and Alcohol Dependence, 120(1-3):22-27. PMID: 22099393. PMCID: PMC3251168.

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65. **Keyes KM**, Schulenberg JE, O'Malley PM, Johnston LD, Bachman JG, Li G, Hasin DS. (2012). Birth cohort effects on adolescent alcohol use: The influence of social norms from 1976-2007. Archives of General Psychiatry, EPub Aug 6. PMID: 22868751. PMCID: PMC3597448.

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73. Robins WR, **Keyes KM**, Utz RL, Martin CL, Yang Y. 2012. Birth cohort effects on abdominal obesity in the United Stets. The Silent Generation, Baby Boomers, and Generation X. International Journal of Obesity, ePub Dec 11. PMID: 23229734. PMCID: PMC3604045.

74. Uddin M, Chang SC, Zhang C, Ressler K, Galea S, **Keyes KM**, McLaughlin K, Wildman DE, Aiello A, Koenen K. 2013. Adcyap1r1 genotype, posttraumatic stress disorder, and depression among women exposed to childhood maltreatment. Depression and Anxiety, ePub Dec 28 2012. PMID: 23280952. PMCID: PMC4081452.

75. Cerda M, Randome Y, **Keyes KM**, Koenen KC, Tardiff KJ, Vlahov D, Galea S. 2013. Prescription opiate mortality trends in New York City, 1990-2006: examining the emergence of an epidemic. Drug and Alcohol Dependence, ePub Jan 25. PMID: 23357743. PMCID: PMC3748247.

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80. Pilowsky D, **Keyes KM**, Geier T, Hasin DS. 2013. Stressful Life Events and Relapse Among Formerly Alcohol Dependent Adults. Social Work in Mental Health, 11(2):184-197. PMID: 24167441. PMCID: PMC3808003.

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87. Kahn S, Okuda M, Hasin DS, Secades-Villa R, **Keyes KM**, Lin K, Grant B, Blanco C. 2013. Gender differences in Lifetime Alcohol Dependence: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Alcoholism: Clinical and Experimental Research, ePub June 13. PMID: 23763329. PMCID: PMC3796956.

88. Carragher N, Krueger RF, Eaton NR, Markon KE, **Keyes KM**, Blanco C, Hasin DS. 2013. ADHD and the externalizing spectrum: direct comparison of categorical, continuous, and hybrid Models of liability in a nationally representative sample. Social Psychiatry and Psychiatric Epidemiology, ePub Oct 1. PMID: 24081325. PMCID: PMC3972373.

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+ mentee
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BOOKS

1. Shrout PE, **Keyes KM**, Ornstein K, eds. 2010. Causality and Psychopathology. Oxford University Press.

2. **Keyes KM**, Galea S. 2014. Epidemiology matters: a new introduction to methodological foundations. New York, Oxford University Press.

    a. Highest-selling epidemiology title in 2014
    b. Used in graduate introductory epidemiology in at least 22 universities worldwide (based on their contact with Keyes and Galea)
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LETTERS TO THE EDITOR/COMMENTARIES

1. Bates L, Barnes D, **Keyes KM**. (2011). Re: Reconsidering the role of social disadvantage in physical and mental health: stressful life events, health behaviors, race, and depression. American Journal of Epidemiology. PMID: 21540321. PMCID: PMC3937594.

2. Wall MM, Poh E, Cerda M, **Keyes KM**, Galea S, Hasin DS. (2012). Commentary on Harper S, Strumph EC, Kaufman JS. Do Medical Marijuana Laws Increase Marijuana Use? Replication Study and Extension. Annals of Epidemiology, 22(7): 536-7. PMID: 22534177. PMCID: PMC3547124.

3. **Keyes KM**, Cerda M. (2013). Racial/ethnic differences in alcohol-related suicide: A call for focus on unraveling paradoxes and understanding structural forces that shape alcohol-related health. Alcoholism: Clinical and Experimental Research, ePub Feb 26. PMID: 23441581. PMCID: PMC5540371.

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9. **Keyes KM**, Susser E. (2014). Expanding the scope of psychiatric epidemiology in the 21st century. Social Psychiatry and Psychiatric Epidemiology, 49(10): 1521-4. PMID: 25096981. PMCID: PMC4167940.

10. **Keyes KM** Susser E, Cheslack-Postava K, Fountain C, Liu K, Bearman PS. 2014. Authors' response: Cohort effects explain the increase in autism diagnosis: an identifiability problem of the age-period-cohort model. International Journal of Epidemiology, 43(5): 1381-8. PMID: 25393200. PMCID: PMC4265900.

11. **Keyes KM**, Barnes D, Bates L. 2015. A letter in response to: Weaver A, Himle JA, Taylor RJ, Matusko NN, Abelson JM. Urban vs Rural Residence and the Prevalence of Depression and Mood Disorder Among African American Women and Non-Hispanic White Women. JAMA psychiatry. PMID: 26561032. PMCID: PMC4671197.

12. Reininghaus U, **Keyes KM**, Morgan C. Novel methods in psychiatric epidemiology. 2016. Soc Psychiatry and Psychiatr Epidemiol. ePub Jun 22. PMID: 27333982. PMCID: PMC4962869.

13. Susser E, Verhulst S, Kark JD, Factor-Litvak PR, **Keyes K**, Magnus P, Aviv A. 2016. Non-Dynamic Association of Depressive and Anxiety Disorders with Leukocyte Telomere Length? American Journal of Psychiatry, 173(11): 1147. PMID: 27798991. PMCID: PMC5325116.

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15. **Keyes KM**, Susser E. 2017. Invited commentary: An ingenious approach to examining the relationship between maternal stress and offspring health? American Journal of Epidemiology, Feb 3, 1-4. PMID: 28158433.

16. **Keyes KM**, Tracy M, Mooney SJ, Shev A, Cerda M. 2017. Invited commentary: Agent-based models: bias in the face of discovery. American Journal of Epidemiology, ePub June 30. PMID: 28673036. PMCID: PMC5860003.

17. **Keyes KM**. 2018. Invited commentary: Marijuana, drug use, and mental health in the United States: a tale of two generations. Addiction, 113(3):482-483. PMID: 29423983.

18. Susser E, **Keyes KM**, Mascayano F. 2018. Health pregnancy and prevention of psychosis. World Psychiatry, 17(3):357-358. PMID: 30192106.

19. Kirkbride JB, **Keyes KM**, Susser E. 2018. City Living and Psychotic Disorders-Implications of Global Heterogeneity for Theory Development. JAMA Psychiatry, ePub Oct 10th. PMID: 30304485.

BOOK CHAPTERS AND SHORT ARTICLES

1. Hasin D, **Keyes KM,** Ogburn E, Hatzenbuehler M. 2007. "Vulnerability to Alcohol and Drug Use Disorders." In M. Tsuang (Ed.), Toward Prevention and Early Intervention of Major Mental and Substance Abuse Disorders. American Psychiatric Publishing, Inc.

2. **Keyes KM,** Hasin DS. 2008. Epidemiology of Alcohol Disorders. In Korsmeyer P & Kranzler H (Eds.), Encyclopedia of Drugs, Alcohol & Addictive Behavior, 3rd edition. Gale Cengage Publishers.

3. **Keyes KM,** Hasin DS. 2008. Causes of alcohol and drug disorders: gender. In Korsmeyer P & Kranzler H (Eds.), Encyclopedia of Drugs, Alcohol & Addictive Behavior, 3rd edition. Gale Cengage Publishers.

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6. Pilowsky D, **Keyes KM**. Women and depression. 2010. In R. Senie (Ed.), Epidemiology of Women's Health. Jones & Bartlett, Publishers.

7. Hasin DS, **Keyes KM.** Epidemiology. 2011. In B. Johnson (Ed.), Addiction Medicine: Science and Practice.

8. **Keyes KM**, Li G. Age-period-cohort analysis in injury epidemiology. 2012. In G. Li & S. Baker (Eds.), Injury Research: Theories, Methods, and Approaches. Springer.

9. **Keyes KM**, Liu X. 2013. Age, period, and birth cohort effects in psychiatric disorders in the United States. In press. In K. Koenen, S. Rudenstine, S. Galea, and E. Susser (Eds.), Life Course Epidemiology of Mental Disorders. Oxford University Press.

10. Fink D, **Keyes K**. Wrong answers. In El-Sayed A, Galea S (Eds.), Systems Science in Population Health. Springer. 2016.

11. Fink D, **Keyes K**, Cerda M. Systems science and social epidemiology. In El-Sayed A, Galea S (Eds.), Systems Science in Population Health. Springer. 2016.

12. Cerda M, **Keyes K**. Longitudinal methods for social epidemiologic research. In J. Kaufman and J.M. Oakes (Eds.), Methods in Social Epidemiology. Jossey-Bass. Expected 2018.

13. **Keyes KM**, Schwartz S, Susser E. Psychiatric Epidemiology. In Rothman, Greenland, Lash, Vanderweele (Eds.), Modern Epidemiology, 4th Edition. Lippincott Williams and Wilkins. Expected 2020.

PRESENTATIONS AND INVITED LECTURES (SELECTED)

Commented [KKM1]: Caroline – charlie wanted these to be separated into "conference presentations" and "invited lectures"

1. Cannabis withdrawal in 2,613 lifetime heavy cannabis users. Symposium presentation, Novel Phenotype Development for Genetics Studies of Substance Abuse Disorders. September 2005, New York, NY.

2. Gender differences in the risk for alcohol abuse and dependence: the effect of birth cohort. Symposium presentation, Psychiatric Epidemiology Faculty/Fellow Training Seminar. December 2005, New York, NY.

3. **Keyes KM**, Hasin DS. Birth cohort effects on gender differences in the risk for drug dependence. College on Problems of Drug Dependence. July 2006, Scottsdale, AZ.
   * **Selected for Women & Gender Junior Investigator Award**

4. Birth cohort effects on gender differences in the risk for alcohol and drug dependence. Symposium presentation, Research Society on Alcoholism. June 2006, Baltimore, MD.

5. Time in the causal landscape: age, period, and cohort effects in alcohol and drug epidemiology. Symposium presentation, Psychiatric Epidemiology Faculty/Fellow Training Seminar. May 2007, New York, NY.

6. Economic capital and problem alcohol use: the positive relationship between income and the DSM-IV alcohol abuse diagnosis. Symposium presentation, Research Society on Alcoholism, July 2007, Chicago, IL.

7. Disentangling age-period-cohort effects: problems and possibilities. Symposium presentation, American Psychopathological Association. March 2008, New York, NY.

8. Methodological Issues in the Estimation of Age-Period-Cohort Effects. Symposium presentation. Psychiatric Epidemiology Faculty/Fellows Training Seminar. March 2008, New York, NY.

9. Influence of a drinking quantity and frequency measure on the prevalence and demographic correlates of DSM-IV alcohol use disorders. Symposium presentation, Research Society on Alcoholism. June 2008, Washington, DC.

10. A Comprehensive Approach to Age-Period-Cohort Analysis. Plenary session presentation, Society for Epidemiologic Research. June 2008, Chicago, IL.

11. Age-Period-Cohort estimation throughout history: tracing the meaning of a 'cohort effect' Symposium presentation. Psychiatric Epidemiology Faculty/Fellows Training Seminar. February 2009, New York, NY.

12. Challenging the paradigm of a "telescoping" phenomenon in gender differences for substance disorders: results of a cohort analysis in the U.S. population. Symposium presentation, International Federation of Psychiatric Epidemiology. April 2009, Vienna, Austria.

13. Population-level disapproval and the prevalence of substance use: a multi-level age-period-cohort analysis of high-school attending adolescents in the United States, 1976-2008. Symposium presentation, Research Seminars in Epidemiology, October 2009, New York, NY.

14. 'Age Selection of Mortality from Tuberculosis': a re-analysis of Frost on the 70th anniversary of publication. Symposium presentation, American Public Health Association, November 2009, Philadelphia, PA.

15. The role of craving in future classifications of alcohol use disorders. Symposium presentation, Adverse Childhood Experiences, Personality Psychopathology, and Alcohol Disorders. December 2009, New York, NY.

16. Time as a multi-level risk factor: the impact of time period- and birth cohort-specific social norms on adolescent marijuana use, 1976-2007. Symposium presentation, École Des Hautes Études En Santé Publique, January 2010, Paris, France.

17. *Time in the causal landscape: problems and possibilities in age-period-cohort research. Survey Research Center, February 2010, Ann Arbor, Michigan.

18. Adverse childhood events and the structure of common psychiatric disorders. Symposium presentation, Adverse Childhood Experiences, Personality Psychopathology, and Alcohol Disorders. May 2010, New York, NY.

19. A multi-level framework for understanding birth cohort effects. Symposium presentation, Research Society on Alcoholism, June 2010, San Antonio, Texas.

20. Novel Methods to Assess Societal-Level Causes of Alcohol Disorders Across Time and Place. Symposium chair, Research Society on Alcoholism, June 2010, San Antonio, Texas.

21. Testing the 'Jackson hypothesis': are black/white differences in depression due to differential effects of stress and unhealthy behaviors? Symposium presentation, Psychiatric Epidemiology Faculty/Fellows Training Seminar. November 2010, New York, NY.

22. *The Epidemiology of Substance Use Disorders. Sexuality and HIV Seminar, HIV Center for Clinical and Behavioral Science. February 2011, New York, NY

23. Methodological issues in the assessment of adverse childhood events. Symposium chair, Society for Epidemiologic Research, June 2011, Montreal, Canada.

24. Childhood Maltreatment and the Structure of Common Psychiatric Disorders. Symposium presentation, Society for Epidemiologic Research, June 2011, Montreal, Canada.

25. Time Trends and Their Explanations. Symposium chair, Research Society on Alcoholism, June 2011, Atlanta, Georgia.

26. Understanding family-based designs using Directed Acyclic Graphs. Symposium presentation, World Psychiatric Association Epidemiology Section, March 2012, Sao Paulo, Brazil.

27. *Time trends in alcohol use: Understanding cohort effects, Adult Psychiatry Grand Rounds, Columbia University Department of Psychiatry, May 2012, New York, NY.

28. Thought disorders in the meta-structure of psychopathology. Symposium presentation, Research Society on Alcoholism, June 2012, San Francisco, CA.

29. How can thought disorders be conceptualized in the meta-structure of psychopathology? Symposium presentation, Life History Society, October 2012, Surrey, England.

30. Comorbidity of less common psychiatric disorders in the meta-structure of psychopathology. Symposium presentation, World Psychiatric Association, October 2012, Prague, Czech Republic.

31. The social norms of birth cohorts: age, period, and cohort effects in adolescent and adult binge drinking. Symposium presentation, Society for Research on Child Development, October 2012, Tampa, FL.

32. *The critical role of social norms in population health. Symposium presentation, Columbia University Epidemiology Scientific Symposium: Charting the Course of Social Epidemiology in the Next 25 Years, Symposium presentation, October 2012, New York, NY.

33. The burden of loss: unexpected death and psychiatric disorders across the life course. International Society for Traumatic Stress Studies, Symposium presentation, November 2012, Los Angeles, CA.

34. *Age, period, and cohort effects: an introduction to theory and approaches to analysis. University of Manitoba Clinical Health Sciences, Department of Psychiatry, Invited lecture, January 2013, Winnipeg, Canada.

35. *How does exogenous and endogenous hormone variation affect mental health? New designs for old problems. Psychiatric-Neurological Epidemiology Cluster Seminar, Invited lecture, Columbia University, February 2013, New York, NY.

36. *Social norms and alcohol use: evidence and recommendations for New York City. Community Services Board Meeting, Invited lecture, New York City Department of Health, March 2013, New York, NY.

37. New Methods for an Old Epidemiologic Problem: Age, Period, and Cohort Effects. Society for Epidemiologic Research, Symposium chair, June 2013, Boston, MA.

38. Racial/ethnic differences in alcohol-attributable homicide: how do we move forward? Society for Epidemiologic Research, Symposium presentation, June 2013, Boston, MA.

39. Early life stress and adult psychiatric disorders: assessing causation in a sea of correlation. Society for Epidemiologic Research, Symposium presentation, June 2013, Boston, MA.

40. Understanding substance use epidemiology across time, space, and generation. Society for Epidemiologic Research, Symposium chair, June 2013, Boston, MA.

41. Racial/ethnic differences in drinking in the US: paradoxes, problems, and research priorities. Research Society on Alcoholism, Symposium chair and presentation, June 2013, Orlando, FL.

42. Understanding the teenage brain in context: 35 years of adolescent sensation seeking in the United States. International Federation of Psychiatric Epidemiology, Symposium chair and presentation, June 2013, Leipzig, Germany.

43. Maternal alcohol consumption and offspring psychopathology. European Public Health Association Conference, Symposium presentation, November 2013, Brussels, Belgium.

44. *Age, period, and cohort effects: an introduction to theory and approaches to analysis. CUNY School of Public Health Epidemiology and Biostatistics Seminar Series, Invited lecture, November 2013, New York, NY.

45. Multi-national birth cohort trends in sensation seeking in the United States from 1976 to 2011. Symposium presentation, Society for Research on Adolescents, March 2014, Austin, TX.

46. *Social norms, attitudes, and behavior: how do we harness intention for public health prevention? Columbia University Epidemiologic Science Symposium, April 2014, New York, NY

47. *How can we intervene in neighborhoods to reduce racial/ethnic inequalities in alcohol-related homicide? Simulating in-silico counterfactuals. Innovations in Translating Injury Research Into Effective Prevention, May 2014, New York, NY.

48. *How can we intervene in neighborhoods to reduce racial/ethnic inequalities in alcohol-related homicide? Simulating in-silico counterfactuals. Partnership for a Healthier New York City, June 2014, New York, NY.

49. How should we prioritize 'external validity' when aiming to conduct an epidemiology that matters? Symposium presentation, Society for Epidemiologic Research, June 2014, Seattle, WA.

50. Health within and across generations: new research in life course epidemiology. Symposium chair, Society for Epidemiologic Research, June 2014, Seattle, WA.

51. *A brief introduction to age-period-cohort methodology. SER Experts presentation, Society for Epidemiologic Research, June 2014, Seattle, WA.

52. Racial/ethnic differences in alcohol use across the life course: an explanation of health disparities? International Epidemiological Association, August 2014, Anchorage, AL.

53. Trajectories of alcohol and cigarette use across the lifecourse: evidence from a pregnancy cohort. Symposium presentation, World Psychiatric Association, September 2014, Madrid, Spain.

54. *The burden of loss: unexpected death and psychiatric disorders across the life course. Symposium presentation, World Psychiatric Association Epidemiology Section, October 2014, Nara, Japan.

55. *Psychiatric disorders among bereaved individuals. Grand Rounds speaker, Hartford Hospital Institute of Living, October 2014, Hartford, CT.

56. *Racial/ethnic differences in substance use across the life course. Grand Rounds speaker, Alcohol Research Group. November 2014, Berkeley, California.

57. Has the population prevalence of adolescent sensation seeking and its relation to substance use changed over time? Symposium presentation, Society for Research on Child Development. March 2015, Philadelphia, PA.

58. The Great Sleep Recession: Changes in Sleep Duration Among US Adolescents, 1991-2012. Symposium presentation, Society for Research on Child Development. March 2015, Philadelphia, PA.

59. Alcohol Interventions and Rates of Violence and Homicide in New York City: an Agent-Based Approach. Symposium presentation, Society for Epidemiological Research, June 2015, Denver, CO.

60. The mathematical limits of genetic prediction for complex chronic disease. Symposium presentation, Society for Epidemiological Research, June 2015, Denver, CO.

61. Teaching epidemiology by building on foundational concepts. Symposium presentation, Society for Epidemiological Research, June 2015, Denver, CO.

62. Mental Health and Aging: Chronic Disease, Cognition, and Pathways Connecting Mind and Body. Symposium chair, Society for Epidemiological Research, June 2015, Denver, CO.

63. *Advances in age, period, and cohort effect analysis. Faculty of Health Sciences Research Seminar Series, Invited lecture, September 2015, Vancouver, Canada.

64. *How and why do psychiatric disorders change across time. Canadian Association of Psychiatric Epidemiology, Keynote speaker, September 2015, Vancouver, Canada.

65. Anxious and angry: course and comorbidity of intermittent explosive disorder and anxiety disorders in adolescence. Symposium presentation, International Federation of Psychiatric Epidemiology, October 2015, Bergen, Norway.

66. *Using complex systems modeling to examine alcohol-attributable homicide in New York City. Invited lecture, Injury Prevention Research Center, Office of the Vice-Chancellor for Research, Social Epidemiology Program, Epidemiology Department, Gillings School of Global Public Health, University of North Carolina. October 2015, Chapel Hill, NC.

67. *How and why do psychiatric disorders change across time. Institute for Translational Epidemiology, Mount Sinai School of Medicine, Seminar presentation, January 2016, New York, NY.

68. *The mathematical limits of genetic prediction for complex chronic disease. Symposium presentation, American Psychopathological Association, March 2016, New York, NY.

69. *Cohort studies in epidemiology: considering cross-generational influences on health. Invited speaker, World Psychiatric Association Epidemiology Section, April 2016, Munich, Germany.

70. How healthy are survey respondents compared to the general population? A comparison of mortality rates from linked death records. Symposium presentation, World Psychiatric Association Epidemiology Section, April 2016, Munich, Germany.

71. *How and why do psychiatric disorders change across time. Brain Health Colloquium, Harvard T.H. Chan School of Public Health, Seminar presentation, April 2016, Boston, MA.

72. How similar are survey respondents to the general population? Symposium presentation, Society for Epidemiologic Research, June 2016, Miami, FL.

73. Agent-Based models and the G-Formula: Comparable Approaches for Evaluating Population Intervention Effects? Symposium discussant, Society for Epidemiologic Research, June 2016, Miami, FL.

74. The impact of traumatic experiences across diverse populations: causes, consequences, and correlates. Symposium chair, Society for Epidemiologic Research, June 2016, Miami, FL.

75. Agent-based model of alcohol taxation effects on violence and homicide in New York City. Symposium presentation, Research Society on Alcoholism, June 2016, New Orleans, LA.

76. *Alcohol use and morbidity across historical time: what does variation tell us about environmental determinants of alcohol-related outcomes? Plenary talk, Research Society on Alcoholism, June 2016, New Orleans, LA.

77. *Why does epidemiology matter? Invited lecture, International Journal of Epidemiology Conference, October 2016, Bristol, UK.

78. *The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Population Health Research Seminar, October 2016, New York University, New York, NY.

79. *The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Epidemiology Seminar Series, November 2016, Virginia Commonwealth University, Richmond, Virginia

80. *Fundamentals of age-period-cohort analysis. Epidemiology Seminar Series, February 2017, University of California San Francisco, San Francisco, California.

81. *The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Epidemiology Seminar Series, April 2017, University of Capetown, Capetown, South Africa.

82. *The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Key note address, Epidemiology Student Research Day, April 2017, McGill University, Montreal, Canada.

83. *Alcohol use and morbidity across historical time: what does variation tell us about environmental determinants of alcohol-related outcomes? National Institute of Health Director's Wednesday Afternoon Lecture Series (WALS), May 2017, NIH, Bethesda, MD.

84. Fifty years of high impact epidemiological research on drug use disorders and related conditions: Looking back and ahead. Symposium presentation, Society for Epidemiologic Research, June 2017, Seattle, WA.

85. Psychiatric epidemiology in the era of precision medicine: what is our role? Symposium chair, Society for Epidemiologic Research, June 2017, Seattle, WA.

86. *The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Seminar Series, August 2017, National Institute of Occupational Health, Oslo, Norway.

87. *Historical and current trends in adolescent heavy alcohol use, depressive affect, and their relationship: implications for adolescent suicide in the United States. NIAAA Workshop to Explore Research Needs in Addressing Alcohol-Related Suicide, September 2017, National Institute of Alcohol Abuse and Alcoholism, Rockville, Maryland.

88. The influence of medical marijuana laws on adolescent and adult outcomes: current state evidence from the United States. Symposium presentation, World Psychiatric Association, October 2017, Berlin, Germany.

89. Utilising epidemiology to guide innovative prevention for comorbid mental and substance use problems in young people. Symposium discussant, International Federation of Psychiatric Epidemiology, October 2017, Melbourne, Australia.

90. Transdiagnostic psychiatric disorder risk associated with early and late age of menarche: a latent modeling approach. Symposium presentation, International Federation of Psychiatric Epidemiology, October 2017, Melbourne, Australia.

91. Mental health and firearm violence: Understanding social and environmental contexts on the path to prevention. Symposium chair, International Federation of Psychiatric Epidemiology, October 2017, Melbourne, Australia.

92. Mental health and firearm violence: what role should disqualification criteria on firearm ownership play? Symposium presentation International Federation of Psychiatric Epidemiology, October 2017, Melbourne, Australia.

93. *The epidemiology of opioid use, opioid disorder, and overdose in the United States: past, present, and evidence-based control strategies. Keynote address, Kentucky Association of Counties annual conference, November 2017, Louisville, Kentucky

94. *As adolescent substance use declines, depression and suicidality increase: a tale across generations. NYU Population Health, Epidemiology Seminar Series. December 4th, 2017, New York, NY

95. *Life Course Psychopathology: The Next Decade. American Psychopathological Association, invited talk, March 3rd, 2018. New York, NY.

96. *Mental health over the life course: adolescence. National Academy of Sciences workshop: Women's Mental Health across the Life Course. March 7th, 2018. Washington DC.

97. *The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Seminar Series, April 2017, French National Institute of Health and Medical Research (INSERM), Paris, France.

98. *Opioid use, disorder, and mortality: past, present, and evidence-based control strategies. Mass Torts Made Perfect conference, invited talk, April 2018, Las Vegas, NV.

99. Declines in the relationship between adolescent depressive affect and binge drinking: implications for public mental health. Research Society on Alcoholism, symposium presentation, June 2018, San Diego, CA.

100. Who thinks like that? Survey methods for non-survey data. Society for Epidemiological Research, symposium presentation, June 2018, Baltimore, MD.

101. Are urban and rural health differences due to exposure prevalence variation or interaction: when and why does it matter? Society for Epidemiological Research, symposium presentation, June 2018, Baltimore, MD.

102. Consequences of medical and recreational cannabis legislation on opioid-related harm. Society for Epidemiological Research, symposium presentation, June 2018, Baltimore, MD.

103. Changes in United States health policy: implications for substance use and injury. Society for Epidemiological Research, symposium chair, June 2018, Baltimore, MD.

104. *Depression's got a hold of me: Gender differences and generational trends in alcohol use and mental health among US adolescents and adults. Substance Abuse Epidemiology Training Program seminar, Columbia University, October 2018, New York, NY.

105. *Depression's got a hold of me: Gender differences and generational trends in alcohol use and mental health among US adolescents and adults. Epidemiology and Biostatistics Seminar, Drexel University, November 2018, Philadelphia, PA.

106. *Depression's got a hold of me: Gender differences and generational trends in alcohol use and mental health among US adolescents and adults. Epidemiology and Biostatistics Seminar, Drexel University, November 2018, Philadelphia, PA.

107. *Depression's got a hold of me: Gender differences and generational trends in alcohol use and mental health among US adolescents and adults. Centro de Investigación en Sociedad y Salud, Universidad Mayor, November 2018, Santiago, Chile.

* Invited lecture

Katherine Keyes publications 2009-2019

1. +Liu X, **Keyes KM**, Li G. 2014. Work stress and alcohol consumption among adolescents: moderation by family and peer influences. BMC Public Health, 14(1): 1303. PMID: 25523951. PMCID: PMC4301940.
2. Martins SS, Kim JH, Chen LY, Levin D, **Keyes KM**, Cerda M, Storr CL. (2014). Nonmedical prescription drug use among US young adults by educational attainment. Social Psychiatry and Psychiatric Epidemiology, ePub Nov 27. PMID: 25427665. PMCID: PMC4405452.
3. Chang HY, **Keyes KM**, Mok Y, Jung KJ, Shin YJ, Jee SH. 2015. Depression as a risk fact+or for overall and hormone-related cancer: The Korean cancer prevention study. J Affect Disorder, ePub March 1. PMID: 25462388. PMCID: PMC4402221.
4. **Keyes KM**, Vo T, Wall M, Caetano R, Suglia SF, Martins SS, Galea S, Hasin DS. (2014). Racial/ethnic differences in use of alcohol, tobacco, and marijuana: Is there a cross-over from adolescence to adulthood? Social Science and Medicine, ePub Nov 18. PMID: 25461870. PMCID: PMC4391514.
5. Kovess V, **Keyes KM**, Pez O, Bitfoi A, Eke C, Golitz D, Kuijpers R, Lesinskiene S, Mihova Z, Otten R, Fermanian C, Pilowsky DJ, Susser E. (2014). Maternal smoking and offspring hyperactivity: results from a cross-national European survey. European Journal Child and Adolescent Psychiatry, European Journal of Child and Adolescent Psychiatry, ePub Nov 21. PMID: 25413602. PMCID: PMC4440844.
6. Taillieu TL, Afifi TO, Mota N, **Keyes KM**, Sareen J. (2014). Age, Sex, and Racial Differences in Harsh Physical Punishment: Results from a Nationally Representative United States Sample. Child Abuse and Neglect, So145-2134(14). PMID: 25466426. PMCID: PMC4402223.
7. +Lee E, **Keyes KM**, Bitfoi A, Zlatka, M, Pez O, Yoon E, Kovess Masfety, V. (2014). Mental health disparities between Roma and non-Roma children in Romania and Bulgaria. BMC Psychiatry, 14(1):297. PMID: 25404375. PMCID: PMC4240804.
8. Hatzenbuehler ML, **Keyes KM**, Uddin M, Hamilton A, Galea S. (2014). The collateral damage of mass incarceration: increased risk of psychiatric morbidity among non-incarcerated residents of high-incarceration neighborhoods. American Journal of Public Health, Nov 12: e1-e6. PMID: 25393200. PMCID: PMC4265900.
9. +Cheslack-Postava K, **Keyes KM**, Lowe S, Koenen K. (2014). Oral Contraceptives are Associated with Reduced Risk of Subthreshold Panic Disorder in a Nationally Representative Sample of U.S. Women. Archives of Women's Mental Health, ePub August 13. PMID: 25113319. PMCID: PMC4308571.
10. **Keyes KM**, Galea S. (2014). Current practices in teaching introductory epidemiology: how we got here, where to go. American Journal of Epidemiology, 180(7): 661-668. PMID: 25190677. PMCID: PMC4481568.
    ***Selected as a 2014 Article of the Year for American Journal of Epidemiology**
11. Lee E, Chang HY, Lee KS, Suh DI, Yu HS, Kang MJ, Choi IA, Park J, Kim KW, Shin YH, Ahn KM, Kwon JY, Choi SJ, Lee KJ, Won HS, Yang SI, Jung YH, Kim HY, Seo JH, Kwon JW, Kim BJ, Kim HB, Lee SY, Kim EJ, Lee JS, **Keyes KM**, Shin YJ, Hong SJ. (2014). The effect of perinatal anxiety on bronchiolitis is influenced by polymorphisms in ROS-related genes. BMC Pulmonary Medicine, 13(1): 154. PMID: 25263840. PMCID: PMC4196140.
12. **Keyes KM**, Susser E, Pilowsky DJ, Hamilton A, Pez O, Bitfoi A, Koc C, Golitz D, Kuijpers R, Lesinkiene S, Mihova Z, Otten R, Kovess V. (2014). The health consequences of child mental health problems and parenting styles: Unintentional injuries among European schoolchildren. Preventive Medicine, ePub Jul 26. PMID: 25073079. PMCID: PMC4409127.

13. Tu Y, **Keyes KM**, Davey Smith G. (2014). Mortality cohort effects from mid 19th to mid 20th century Britain: did they exist? Annals of Epidemiology, 24(8): 570-4. PMID: 25084701. PMCID: PMC4402224.
14. Kim J, Martins S, Shmulewitz D, Santaella J, Wall M, **Keyes KM**, Eaton N, Krueger RF, Grant BF, Hasin DS. (2014). Childhood maltreatment, stressful life events, and alcohol craving in adult drinkers. Alcoholism: Clinical and Experimental Research, 38(7):2048-55. PMID: 24961735. PMCID: PMC4107183.
15. Cerda M, Bordelois P, **Keyes KM**, Roberts A, Martins S, Seisner S, Austin S, Corliss H, Koenen K. (2014). Family ties: maternal-offspring attachment and young adult nonmedical prescription opioid use. Drug and Alcohol Dependence, ePub June 30. PMID: 25024105. PMCID: PMC4134317.
16. **Keyes KM**, Nicholson R, Kinley J, Raposo S, Stein M, Goldner E, Sareen J. (2014). Age, period, and cohort effects in psychological distress in the United States and Canada. American Journal of Epidemiology, ePub May 15. PMID: 24692432. PMCID: PMC4010185.
17. **Keyes KM**, Pratt C, McLaughligh K, Galea S, Koenen K, Shear K. (2014). The Burden of Loss: Unexpected death of a loved one and psychiatric disorders across the life course in a national study. American Journal of Psychiatry, ePub May 16, PMID: 24832609. PMCID: PMC4119479.
18. Welch AE, Caramanica K, Maslow CB, Cone JE, Farfel MR, **Keyes KM**, Stellman SD, Hasin DS. (2014). Frequent binge drinking five to six years after exposure to 9/11: Findings from the World Trade Center Health Registry. Drug and Alcohol Dependence, ePub Apr 28, PMID: 24831753. PMCID: PMC4154498.
19. +Barnes D, **Keyes KM**, Hamilton A, Hatzenbuehler ML. (2014). Sexual orientation disparities in mental health: the moderating role of educational attainment. Social Psychiatry and Psychiatric Epidemiology, ePub Feb 26. PMID: 24570204. PMCID: PMC4145056.
20. Hatzenbuehler ML, **Keyes KM**, Hamilton A, Hasin DS. (2014). State-Level Tobacco Environments and Sexual Orientation Disparities in Tobacco Use and Dependence in the United States. Tobacco Control, ePub Feb 25. PMID: 24570099. PMCID: PMC4386615.
21. +Lukachko A, Hatzenbuehler M, **Keyes KM***. (2014). Structural racism and myocardial infarction in the United States. Social Science and Medicine, 103:42-50. PMID: 24507909. PMCID: PMC4133127.
22. Elliott J, Stohl M, Wall M, **Keyes KM**, Goodwin R, Skodol A, Krueger R, Grant BF, Hasin D. (2014). The risk for persistent adult alcohol and nicotine dependence: the role of childhood maltreatment. Addiction, ePub Jan 8. PMID: 24401044. PMCID: PMC3984602.
23. **Keyes KM**, Cerda M, Brady J, Havens J, Galea S. (2013). Understanding the rural-urban differences in nonmedical prescription opioid use and abuse in the United States. American Journal of Public Health, ePub Dec 12. PMID: 24328642. PMCID: PMC3935688.
24. +Chang HY, **Keyes KM**, Lee K, Choi I, Kim SJ, Kim, KW, Shin YH, Ahn KM, Hong S, Shin Y. (2013). The Effect of Prenatal Maternal Depression on Risk of Low Birth Weight, Gestational Age, and Weight for Gestational Age in Term Infants in Korea. Early Human Development, ePub Dec 10. PMID: 24331828.
25. Ananth CV, **Keyes KM**, Wapner RJ. (2013). Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. British Medical Journal, ePub Nov 7. PMID: 24201165. PMCID: PMC3898425.
26. **Keyes KM**, Shmulewitz D, Greenstein E, McLaughlin M, Wall M, Aharonovich E, Weizman A, Frisch A, Spivak B, Grant BF, Hasin DS. 2013. Exposure to the Lebanon War of 2006 and effects on alcohol use disorders: The moderating role of childhood maltreatment. Drug and Alcohol Dependence, ePub Oct 31. PMID: 24262650. PMCID: PMC3884580.

27. +Platt J, **Keyes KM**, Koenen K. 2013. Size of social network versus quality of social support: which is more protective against PTSD? Social Psychiatry and Psychiatric Epidemiology, ePub Dec 6. PMID: 24310782.
28. Cerda M, Randome Y, **Keyes KM**, Koenen KC, Tardiff KJ, Vlahov D, Galea S. 2013. Revisiting the role of the urban environment in substance use. The case of analgesic overdose fatalities. American Journal of Public Health, ePub Oct 17. PMID: 24134362. PMCID: PMC3828967.
29. Kilpatrick D, Resnick HS, Milanak ME, Miler MW, **Keyes KM**, Friedman MJ. 2013. National Estimates of Exposure to Traumatic Events and PTSD Prevalence Using DSM-IV and Proposed DSM-5 Criteria. Journal of Traumatic Stress, 26(5):537-47. PMID: 24151000. PMCID: PMC4096796.
30. Meyers JL, Shmulewitz D, Wall MM, **Keyes KM**, Aharonovich A, Spivak B, Weizman A, Frisch A, Edenberg HJ, Gelernter J, Grant BF, Hasin D. 2013. Childhood adversity moderates the effect of ADH1B on risk for alcohol-related phenotypes in Jewish Israeli drinkers. Addiction Biology, ePub Oct 24. PMID: 24164917. PMCID: PMC3999313.
31. Talati A, Wickramaratne PJ, **Keyes KM**, Hasin DS, Levin F, Weissman MM. Smoking and psychopathology increasingly associated in recent birth cohorts. Drug and Alcohol Dependence, ePub Sep 5. PMID: 24071570. PMCID: PMC3818417.
32. Carragher N, Krueger RF, Eaton NR, Markon KE, **Keyes KM**, Blanco C, Hasin DS. 2013. ADHD and the externalizing spectrum: direct comparison of categorical, continuous, and hybrid Models of liability in a nationally representative sample. Social Psychiatry and Psychiatric Epidemiology, ePub Oct 1. PMID: 24081325. PMCID: PMC3972373.
33. Kahn S, Okuda M, Hasin DS, Secades-Villa R, **Keyes KM**, Lin K, Grant B, Blanco C. 2013. Gender differences in Lifetime Alcohol Dependence: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Alcoholism: Clinical and Experimental Research, ePub June 13. PMID: 23763329. PMCID: PMC3796956.
34. Cerda M, Bordelois PM, **Keyes KM**, Galea S, Koenen KC, Pardini D. 2013. Cumulative and Recent Psychiatric Symptoms as Predictors of Substance Use Onset: Does Timing Matter? Addiction, ePub August 14. PMID: 23941263. PMCID: PMC3833999.
35. Meyers JL, Cerda M, Galea S, **Keyes KM**, Aiello AE, Uddin M, Wildman DE, Koenen K. 2013. Interaction between Polygenic Risk for Cigarette Use and Environmental Exposures in the Detroit Neighborhood Health Study. Translational Psychiatry, ePub August 13. PMID: 23942621. PMCID: PMC3756291.
36. **Keyes KM**, Cheslack-Postava K, Heim C, Westhoff C, Haloosim M, Walsh K, Koenen K. 2013. Association of Hormonal Contraceptive Use with Reduced Levels of Depressive Symptoms: A National Study of Sexually Active Women in the United States. American Journal of Epidemiology, ePub Sept 15. PMID: 24043440. PMCID: PMC3888252.
37. Hatzenbuehler M, **Keyes KM**. 2013. Inclusive anti-bullying policies and reduced risk of suicide attempts in lesbian and gay youth. Journal of Adolescent Health, 53, S21-S26. PMID: 23790196. PMCID: PMC3696185.
38. +Barnes D, **Keyes KM**, Bates L. Racial differences in depression in United States: How do subgroup analyses inform a paradox? Social Psychiatric and Psychiatric Epidemiology, ePub Jun 4. PMID: 23732705. PMCID: PMC3834079.
39. **Keyes KM**, Davey Smith G, Susser E. 2013. Associations of prenatal maternal smoking and offspring hyperactivity: causal or confounded? Psychological Medicine, ePub May 15. PMID: 23676207. PMCID: PMC4615686.
40. Pilowsky D, **Keyes KM**, Geier T, Hasin DS. 2013. Stressful Life Events and Relapse Among Formerly Alcohol Dependent Adults. Social Work in Mental Health, 11(2):184-197. PMID: 24167441. PMCID: PMC3808003.

41. **Keyes KM**, McLaughlin K, Demmer R, Cerda M, Koenen K, Uddin M, Galea S. 2013. Potentially traumatic events and the risk of six physical health conditions in a population-based sample. Depression and Anxiety, ePub March 11. PMID: 23495094. PMCID: PMC4180235.
42. **Keyes KM**, Miech R. 2013. Age, period, and cohort effects in heavy episodic drinking in the US from 1985-2009. Drug and Alcohol Dependence, ePub Feb 20. PMID: 23433898. PMCID: PMC4827021.
43. Katz C, El-Gabalawy R, **Keyes KM**, Martins SS, Sareen J. 2013. Risk factors for incident nonmedical prescription opioid use and abuse and dependence: Results from a longitudinal nationally representative sample. Drug and Alcohol Dependence, ePub Feb 8. PMID: 23399466.
44. +Fenton MC, Geier T, **Keyes KM**, Skodol AE, Grant BF, Hasin DS. 2013. Combined role of childhood maltreatment, family history, and gender in the risk for alcohol dependence. Psychological Medicine, 43(5):1045-1057. PMID: 22883538. PMCID: PMC3767412.
45. Cerda M, Randome Y, **Keyes KM**, Koenen KC, Tardiff KJ, Vlahov D, Galea S. 2013. Prescription opiate mortality trends in New York City, 1990-2006: examining the emergence of an epidemic. Drug and Alcohol Dependence, ePub Jan 25. PMID: 23357743. PMCID: PMC3748247.
46. Uddin M, Chang SC, Zhang C, Ressler K, Galea S, **Keyes KM**, McLaughlin K, Wildman DE, Aiello A, Koenen K. 2013. Adcyap1r1 genotype, posttraumatic stress disorder, and depression among women exposed to childhood maltreatment. Depression and Anxiety, ePub Dec 28 2012. PMID: 23280952. PMCID: PMC4081452.
47. Robins WR, **Keyes KM**, Utz RL, Martin CL, Yang Y. 2012. Birth cohort effects on abdominal obesity in the United Stets. The Silent Generation, Baby Boomers, and Generation X. International Journal of Obesity, ePub Dec 11. PMID: 23229734. PMCID: PMC3604045.
48. **Keyes KM**, March D, Link BG, Chilcoat HD, Susser E. Do socio-economic gradients in smoking emerge differently among women? Implications for the tobacco epidemic. Social Science and Medicine, ePub Nov 8th. PMID: 23186639. PMCID: PMC3612831.
49. Shmulewitz D, Wall MM, **Keyes KM**, Aharonovich E, Aivadyan C, Greenstein E, Spivak B, Weizman A, Frisch A, Hasin DS. (2012). Alcohol use disorders and perceived drinking norms: ethnic differences in Israeli adults. Journal of Studies on Alcohol and Drugs, 73(6): 981-990. PMID: 23036217. PMCID: PMC3469051.
50. Eaton NR, **Keyes KM**, Krueger RF, Noordhof A, Skodol AE, Markon KE, Grant BF, Hasin DS. (2012). Ethnicity and psychiatric comorbidity in a national sample: evidence for latent comorbidity factor invariance and connections with disorder prevalence. Social Psychiatry and Psychiatric Epidemiology, ePub Sep 30. PMID: 23052426. PMCID: PMC3562755.
51. **Keyes KM**, Eaton N, Krueger RF, Wall M, Skodol A, Siever L, Grant BF, Hasin DS. (2012). Thought Disorder in the meta-structure of psychopathology. Psychological Medicine, ePub Nov 21. PMID: 23171498. PMCID: PMC3767418.
52. **Keyes KM**, Hatzenbuehler M, Grant BF, Hasin D. (2012). Stress and Alcohol: Epidemiologic Evidence. Alcohol Research: Current Reviews, 34(4): 391-400. PMID: 23584105. PMCID: PMC3797525.
53. Eaton N, Krueger RF, Markon K, **Keyes KM**, Skodol AE, Wall M, Hasin DS, Grant BF. (2012). The Structure, Continuity, and Predictive Validity of the Internalizing Disorders. Journal of Abnormal Psychology, Epub: Aug 20. PMID: 22905862. PMCID: PMC3755742.
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55. **Keyes KM**, Schulenberg JE, O'Malley PM, Johnston LD, Bachman JG, Li G, Hasin DS. (2012). Birth cohort effects on adolescent alcohol use: The influence of social norms from 1976-2007. Archives of General Psychiatry, EPub Aug 6. PMID: 22868751. PMCID: PMC3597448.

56. Goodwin RD, Zvolensky MJ, **Keyes KM**, Hasin DS. (2012). Mental disorders and cigarette use among adults in the United States. American Journal on Addictions, 21(5):416-423. PMID: 22882392. PMCID: PMC3701304.
57. +Fenton M, **Keyes KM**, Geier T, Greenstein E, Skodol A, Krueger RF, Hasin D. 2012. Psychiatric comorbidity and the persistence of drug use disorders in the United States. Addiction, 107(3):599-609, PMID: 21883607. PMCID: PMC3260401.
58. Cerda M, Wall M, **Keyes KM**, Galea S, Hasin DS. 2012. Medical marijuana laws in 50 states: investigating the impact of state legalization of medical marijuana and marijuana use, abuse and dependence. Drug and Alcohol Dependence, 120(1-3):22-27. PMID: 22099393. PMCID: PMC3251168.
59. Robinson WC, Martin C, **Keyes KM**, Utz R, Yang Y. 2012. Birth cohort effects among US-born adults born in the 1980s: foreshadowing future trends in US obesity prevalence. International Journal of Obesity, Epub May 1. PMID: 22546778. PMCID: PMC3448850.
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62. McLaughlin K, Nandi A, **Keyes KM**, Uddin M, Aiello AE, Galea S, Koenen KC. 2011. Home foreclosure and risk of psychiatric morbidity during the recent financial crisis. Psychological Medicine, ePub Nov 21. PMID: 22099861. PMCID: PMC3438142.
63. Hasin DS, Fenton M, Skodal A, Krueger R, **Keyes KM**, Blanco C, Johnson J, Geier T, Grant B. 2011. Personality disorders and the 3-year course of alcohol, drug, and nicotine use disorders. Archives of General Psychiatry, 68(11):1158-1167. PMID: 22065531. PMCID: PMC3500879.
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65. Hankerson SH, Fenton MC, Geier TJ, **Keyes KM**, Weissman MM, Hasin DS. 2011. Racial Differences in Symptoms, Comorbidity, and Treatment for Major Depressive Disorder among Black and White Adults. Journal of the National Medical Association, 103(7):576-84. PMID: 21999032. PMCID: PMC3866690.
66. Martins SS, Fenton MC, **Keyes KM**, Blanco C, Zhu H, Storr CL. 2011. Mood/Anxiety disorders and their association with non-medical prescription opioid use and prescription opioid use disorder: longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions. Psychological Medicine, ePub Oct 17. PMID: 21999943. PMCID: PMC3513363.
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